LONGITUDINAL PATTERNS OF UNMET NEED FOR CONTRACEPTION AND THE EFFECT OF FERTILITY INTENTIONS ON ATTENDANCE AT HIV CLINICAL CARE VISITS AMONG HIV-INFECTED WOMEN ON ANTIRETROVIRAL THERAPY IN SOUTH AFRICA

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ABSTRACT

Katherine B. Rucinski: Longitudinal patterns of unmet need for contraception and the effect of fertility intentions on attendance at HIV clinical care visits among HIV-infected women on antiretroviral therapy in South Africa
(Under the direction of Audrey E. Pettifor)

Fertility intentions and contraceptive use are often not assessed in the context of HIV clinical care, representing a possible gap in many current programs if women's family planning needs change over time. Additionally, women who are planning to conceive have different clinical needs than those what wish to prevent pregnancy, precipitating potential differences in the frequency with which women attend HIV clinical care visits. We used data from a prospective cohort study of 850 non-pregnant, HIV-infected women aged 18-35 on or initiating antiretroviral therapy (ART) in Johannesburg, South Africa between 2009 and 2010. In Aim 1, we used group-based trajectory modeling to identify distinct patterns of unmet need over the 12-month study period. Half of the enrolled women were predicted to have a consistently high probability of unmet need, 22.9% a consistently low probability, 16.7% a decreasing probability, and 10.4% an increasing probability over time. In Aim 2, we estimated the effect of fertility intentions on attendance at HIV clinical care visits. Women were classified as having either current fertility intentions (trying to conceive at time of interview), short-term fertility intentions (planning to conceive in the next 12 months), long-term fertility intentions (planning to conceive in the future) or having no plans to conceive. Attendance was assessed dichotomously (any attendance vs. none) in 90-day intervals. We used generalized estimating equations to estimate the effect of fertility intentions on the odds of attending clinic visits over the 12-month study period. We found no difference in clinic attendance by fertility intentions in the full cohort.

Among women who had recently initiated ART, those that planned to conceive were more likely to attend HIV clinical care visits (aOR 2.95, 95% CI: 1.19, 7.30) than those with no plans to conceive. Through this research we have demonstrated that family planning needs can change over time and thus should be assessed more regularly in HIV-infected women.

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For Tim, Trudy and Leah

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This dissertation includes data that were originally collected over a three-year period in Johannesburg, South Africa through the Wits Reproductive Health and HIV Institute. I am especially appreciative of the study staff and women that participated in this research, without whom this dissertation would not be possible. I am also indebted to Sheree Schwartz for allowing me use of these data, and for her invaluable support and overall contribution to this research. I would also like to offer thanks to all my committee members for their continued patience and guidance throughout this process. Finally, I am grateful to both the Society of Family Planning Research Fund and ViiV Healthcare for their financial support of this dissertation.

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LIST OF ABBREVIATIONS

ACASI	audio-computer assisted self-interview
AIDS	acquired immunodeficiency syndrome
ANC	antenatal care
ART	antiretroviral therapy
BIC	Bayesian information criterion
CDC	Centers for Disease Control and Prevention
CI	confidence interval
DAG	directed acyclic graph
GEE	generalized estimating equation
GBTM	group-based trajectory modeling
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
IQR	interquartile range
LRT	likelihood ratio test
LTFU	loss to follow-up
MI	multiple imputation
MTCT	mother-to-child HIV transmission
OR	odds ratio (aOR adjusted odds ratio)
PMTCT	prevention of mother-to-child HIV transmission
UPT	urine pregnancy test
UTT	universal test and treat
WHO	World Health Organization

CHAPTER I: SPECIFIC AIMS

With expanded access to affordable antiretroviral therapy (ART) in sub-Saharan Africa and the recommendation of earlier thresholds for treatment initiation,[1] HIV-infected women on ART are living longer healthier lives.[2] For HIV-infected women on ART, using reliable methods of contraception to plan pregnancy when CD4 count is high and viral load is low benefits maternal health and contributes to the prevention of mother-to-child HIV transmission (PMTCT).[3-5] However, despite growing recognition for greater integration of sexual and reproductive health services with HIV prevention, care, and treatment services,[6] HIV-infected women still face difficulties meeting their contraceptive needs.[7,8]

In South Africa, high incidence of unplanned pregnancy among women taking ART warrants a better and more nuanced understanding of the long-term changes in unmet contraceptive need that occur in the period following ART initiation.[5] Identification of temporal trends in unmet need for contraception amidst ART scale-up could characterize novel opportunities to increase contraceptive use and strengthen integrated family planning and HIV programs.

Successful expansion and implementation of ART also depends on maximizing the proportion of HIV-infected women who are engaged in HIV care.[9] Loss to follow-up and low levels of ART adherence impede efforts to optimize treatment outcomes in HIV-infected patients.[10] Myriad physical and psychosocial barriers to engagement in care have been identified among HIV-infected women,[9,11-26] including pregnancy status.[26-29] Pregnancy is associated with sub-optimal engagement in care among women who initiate ART through PMTCT;[26,27] however rates of retention are markedly higher among women who initiate ART for

their own health.[28,29] Health-seeking behaviors in HIV-infected women are in part motivated by maternal concerns regarding fetal health,[9,11,24,28,30] and the desire to have an HIV-negative child may motivate women to remain engaged in care. Similarly, women trying to become pregnant may be motivated by horizontal transmission concerns to have a more consistent relationship with HIV care than women who are not trying to conceive. However, the relationship between fertility intentions and retention in care is not well understood.

In this study, we leveraged a unique, observational cohort of HIV-infected women taking ART in South Africa to better characterize patterns of unmet need for contraception and the relationship between fertility intentions and engagement in HIV care. Data were prospectively collected from 850 women at repeat study visits over a one-year period at two ART initiation sites and two ART down-referral sites in Johannesburg. The specific aims of this study were to 1) Describe longitudinal changes in unmet need for contraception following ART initiation and 2) Estimate the causal effect of fertility intentions on attendance at HIV clinical care visits.

To address aim 1, we used group-based trajectory modeling to characterize changes in unmet need for contraception and identify factors that both predict and alter the developmental course of the outcome over the study period.[31] **To address aim 2,** generalized linear models fit using generalized estimating equations (GEE) were used to compare the odds of attending clinic visits among women trying and not trying to conceive.

Data from this cohort are well published,[5,32,33] and indicate high rates of unplanned pregnancy among HIV-infected women after ART initiation.[5] This study expands on these initial findings by 1) providing a nuanced and previously unexplored long-term assessment of unmet need for contraception and 2) evaluating the causal relationship of fertility intentions with attendance at HIV clinical care visits. Through this research, we have identified potential opportunities for integrated contraceptive and HIV counseling that may ultimately improve maternal wellbeing and prevent HIV transmission.

CHAPTER II: BACKGROUND

An estimated 25 million people are living with HIV in sub-Saharan Africa, accounting for more than 70% of all HIV infections worldwide.[34] In South Africa, the majority of people living with HIV are women of reproductive age,[34] and prevalence of HIV among young women is as much as three times that among young men.[28,35] South Africa also has one of the largest national treatment programs in the world, accounting for 20% of all persons on antiretroviral therapy (ART) globally.[36]

1. Aim 1. Longitudinal Patterns of Unmet Need for Contraception

Widespread availability of antiretroviral therapy (ART) – together with expanded programs to promote access to reliable contraception and safer conception methods – have shifted the landscape of reproductive decision-making in sub-Saharan Africa.[1,2,37-39] In South Africa, national service delivery guidelines promote the integration of sexual and reproductive health services with HIV prevention, care and treatment services to strengthen both family planning and HIV-related outcomes.[40] However, implementation of these guidelines in clinical practice has been limited.[41]

Comprehensive programs to reduce unmet need for contraception in HIV-infected women[43] primarily focus on: 1) improving availability of services, 2) increasing education and information dissemination around contraceptive use and 3) improving contraceptive counseling at the provider level.[8,44-47] However, even in settings where these enhanced family planning services are integrated with HIV clinical care visits, heath-facility factors such as high patient volume and a limited number of providers can affect patient-provider interaction time and quality of care.[48,49] Furthermore, negative attitudes towards

childbearing and concerns about mother-to-child transmission may preclude providers from routinely assessing fertility preferences and contraceptive use.[50,51] Consequently, changes in the family planning needs of HIV-infected women may go undetected.

Despite growing recognition for greater integration of sexual and reproductive health services with HIV prevention, care, and treatment services,[6] HIV-infected women still face difficulties meeting their contraceptive needs.[5,7,8,42] Updated guidelines from the World Health Organization (WHO) define population-level unmet need for family planning ("unmet need") as the percentage of "married or in-union women of reproductive age who want to stop or postpone childbearing but who report that they are not using any method of contraception to prevent pregnancy".[52] Unmet need for family planning comprises two groups of women: 1) women with an unmet need for limiting, and 2) women with an unmet need for spacing. Women with an unmet need for limiting are those who desire no additional children and who do not currently use a reliable contraceptive method. Women with an unmet need for spacing are those who desire to postpone their next birth by a specified length of time and who do not currently use a reliable contraceptive method. Persistent barriers to family planning include lack of female decision-making power,[53] poor economic resources,[54] low quality care at family planning services,[55] and desire for large families.[56,57]

Family planning needs among HIV-infected women may differ from those of HIV-uninfected women, particularly in the period following ART initiation. In some cross-sectional studies, fertility intentions and desires have been shown to decrease following the initial diagnosis of HIV[58,59] and rebound in the period following ART initiation.[60-62] However, one longitudinal study in Uganda found that pregnancy desires and hormonal contraception use were not associated with time-on-ART.[63] Still, unmet need for contraception may increase after ART initiation among women whom, after experiencing sub-fertility related to HIV-associated disease progression,[64] fail to realize they are able conceive.[65,66] We conceptualize fertility in HIV-infected women as a complex interplay of biological and behavioral processes that evolve

over the reproductive lifespan (Figure 2.1). At a provider level, careful and routine consideration of these factors may increase the capacity of HIV-infected women to prevent or delay pregnancy until they are clinically stable and virally suppressed, which is largely important for both maternal wellbeing and prevention of mother-to-child transmission (PMTCT).[67-72]

For HIV-infected women taking ART, using reliable methods of contraception to plan pregnancy when CD4 count is high and viral load is low benefits maternal health and contributes to the prevention of mother-to-child HIV transmission (PMTCT).[3-5] Prevention of unplanned pregnancy through reliable contraceptive methods improves women's health and reduces both maternal and infant mortality.[71,72] Prevention of unplanned pregnancy is also an effective strategy to reduce mother-to-child transmission (MTCT) by preventing HIV-infected births,[73] and is the second prong of WHO's four-pronged framework for PMTCT.[74] Indeed, several modeling studies have demonstrated that PMTCT prophylaxis is most effective when implemented in combination with programs to decrease unmet contraceptive need.[73,75] Decreasing the number of infants born to HIV-infected mothers by meeting their contraceptive needs could shift resources to provide more comprehensive monitoring of HIV treatment outcomes among women and children.

Understanding patterns of unmet contraceptive need in HIV-infected women could potentially help providers better identify those who may be at risk for unintended pregnancy. Characterization of temporal trends or predictors of unmet need for contraception could inform more targeted screening practices that are better designed to identify women who will benefit from family planning interventions. In this investigation, we assessed distinct longitudinal patterns of unmet need for contraception over a 12-month period within a cohort of HIV-infected women taking ART in South Africa.

2. Aim 2. Fertility Intentions and Attendance at HIV Clinical Care Visits

ART has been available in South Africa to those who are pregnant or breastfeeding since early 2015,[76] but challenges persist keeping women engaged in care during pregnancy

and the postpartum period. ART coverage is significantly higher in HIV-infected women than in men in South Africa,[36] but significant concerns around adherence and retention have emerged around women who obtain treatment during pregnancy.[77-79] Several studies have reported sub-optimal adherence and high incidence of loss to follow-up (LTFU) among women who initiate ART during pregnancy compared to women who initiate ART for their own health,[26,27,29] especially in the postpartum period.[28,80,81] While factors that cause women to ultimately disengage from HIV care are complex and dynamic,[77] some have hypothesized that women who initiate ART through PMTCT are ultimately less motivated to remain in care in the postpartum period after the risk of mother-to-child transmission has subsided.[24,28,82] Declining adherence in the postpartum period has also been associated with lifestyle stressors and postpartum depression.[28,83-86] Psychosocial barriers to adherence have also been identified, including concerns around disclosure and stigma, alcohol or drug use and drug regimen frequency or pill burden.[18,19,26] However, the relationship between these determinants of care attendance are poorly understood, and the extent to which childbearing decisions impact engagement in care- both in the preconception and postpartum periods- has not been well characterized.

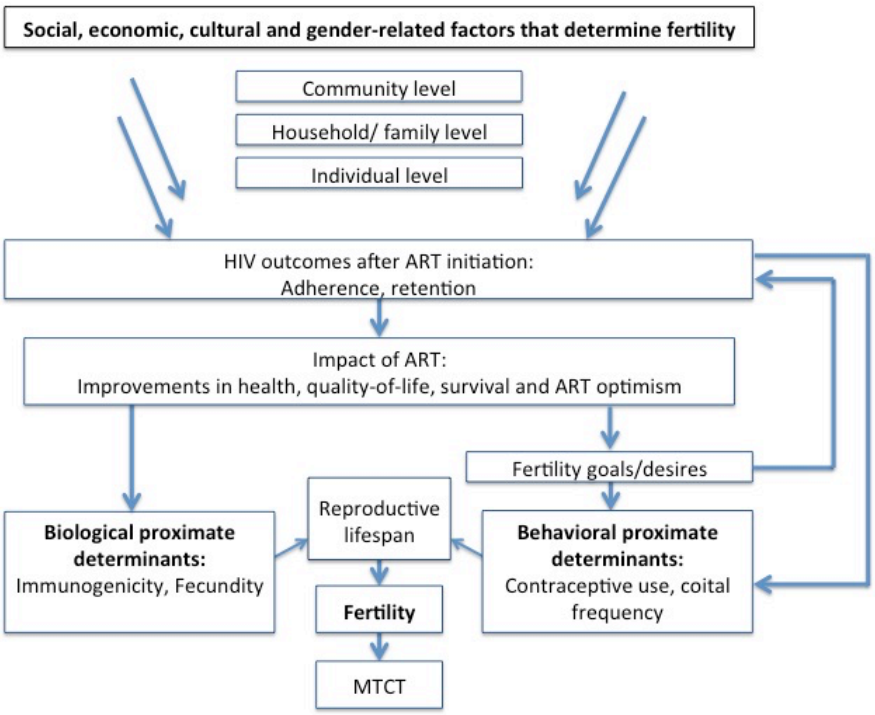
Successful expansion of ART in South Africa- including improved HIV outcomes- will depend on maximizing the proportion of those with HIV who consistently attend their routine clinical care visits and adhere to treatment in the period following diagnosis.[9] Suboptimal retention and low levels of ART adherence impede efforts to optimize treatment outcomes in HIV-infected women.[10] Patients who disengage from care and interrupt treatment are also more likely to have an increased risk of drug resistance, morbidity and mortality.[11,38,87] Rates of loss to follow-up in resource limited settings are consistently high; among patients not yet on ART attrition occurs from the time of testing to completion of CD4 staging,[88,89] from completing staging to repeat CD4 testing for ART eligibility,[90,91] and from ART eligibility to ART

initiation.[90,92,93] For patients who do initiate ART, a high risk of attrition occurs within the first year of treatment.[94-96]

Women who are planning to conceive have different clinical needs than those who wish to prevent pregnancy, precipitating potential differences in the frequency with which women attend HIV clinical care visits. Concerns about horizontal transmission in the preconception period or PMTCT after conception may also motivate women who are planning to conceive to have a more consistent relationship with HIV care. Evidence distinguishing different HIV care patterns among women trying and not trying to conceive could potentially inform new models for care delivery the preconception period. Furthermore, an association between fertility intentions and HIV care attendance in the preconception period could potentially explain differences in care attendance during pregnancy and in the postpartum period. Here, we estimated the effect of fertility intentions on attendance at HIV clinical care visits among HIV-infected women on ART in Johannesburg, South Africa.

3. Tables and Figures

FIGURE 2.1 Conceptual framework for the potential impact of antiretroviral therapy (ART) on fertility among HIV-infected women in sub-Saharan Africa.



Adapted from Kaida, A., et al. (2006)[97]

CHAPTER III: RESEARCH DESIGN AND METHODS

1. Description of Data

1.1 Data Source

This study is a secondary, longitudinal analysis of data collected though a CDC-funded prospective cohort study.[5,32,33] The goals of the original study ("Pregnancy Intentions and Incidence in HIV Positive Women on Antiretroviral Therapy in South Africa") were to: 1) determine the incidence of pregnancy and 2) assess contraceptive use and associations with unplanned pregnancy in HIV-infected women enrolled on ART in Johannesburg, South Africa (Table 3.1). ART is provided free of charge by the Ministry of Health in South Africa based on pregnancy, immunological or clinical status. In early 2016 South Africa announced expanded ART access through universal "test and treat" (UTT) following World Health Organization (WHO) recommendations to initiate ART after HIV diagnosis regardless of disease severity or maternal immunological status.[1] At the time of study enrollment, however, non-pregnant women were eligible for lifelong ART initiation only if they had a CD4 count ≤200 cells/ml or WHO clinical stage 4 diagnosis.

1.2 Recruitment

Enrollment occurred from August 2009 to January 2010 at four government-run ART outpatient clinics in inner city Johannesburg. Clinics included two ART initiation sites and two ART maintenance sites where patients continue treatment once they are clinically stable and responsive to ART. In practice, some patients attending ART initiation sites were previously initiated onto ART and had not been referred to a maintenance site due to patient reluctance to changing facilities, oversight on the clinic's part or potential complications or risks that may

require physician attendance. Both clinic types were included to enroll patients with a diverse group of ART experiences.

Patients were recruited by convenience sample at each of the four study sites over a two to three-month period, depending on when enrollment targets were met. Enrollment targets were site-specific and proportional to clinic size. All women who appeared ≤50 years of age who visited one of the four clinics during the enrollment period were approached and invited by research assistants to participate in a study related to reproductive health and experiences with ART. Interested individuals were provided additional information and underwent further screening. Those meeting eligibility criteria were informed of additional study details and consented to participate (Table 3.1). Consented patients were tested for pregnancy and those who were not pregnant were enrolled in the study.

At the time of study enrollment, approximately 9,000 patients were receiving care at the two ART initiation sites and two ART maintenance sites. Roughly 3,000 (33.3%) of these patients were women who met the study's eligibility criteria. A total of 850 women were targeted for enrollment into the study.

1.3 Study Enrollment and Follow-Up

A total of 850 non-pregnant women with a confirmed HIV diagnosis who were previously on or being initiated onto ART were recruited by convenience sample during routine clinic visits at four government-run ART outpatient clinics in inner city Johannesburg. Women completed an interviewer-administered questionnaire at enrollment (Baseline). Follow-up visits occurred every 1-3 months based on clinic protocol and provincial ART supply, and the median time between visits was 1.8 months [interquartile range (IQR) 1–2]. Participants had a median of six post-enrollment follow-up visits and contributed a median of 12 months [IQR 9–13] of follow-up to the cohort.

Women who did not become pregnant during the study period were followed through the first clinical visit after completing 12 months of follow-up. Women who became pregnant during

the study period were followed through the entirety of their pregnancy, and thus may have contributed greater than 12 months of follow-up.

1.4 Data Collection

Baseline Questionnaire

Interviewer-administered questionnaires were conducted at Baseline in English, Zulu or Sotho to obtain behavioral study data. Questions were asked in the following seven domains:

1. Demographics
2. Health status and fertility history
3. Fertility potential and intentions
4. Sexual behavior and contraception use
5. Fertility desires
6. Perceptions of providers' attitudes towards fertility
7. Relationship dynamics

Follow-Up Questionnaire

Contraceptive use and current fertility intentions were assessed at each follow-up visit via a short interviewer-administered tool in English, Zulu or Sotho. Questions were selected from a comprehensive review of the available literature and piloted prior to enrollment.

Clinical Variables

Pregnancy testing was conducted at Baseline and during each follow-up visit. Pregnancy was determined using urine-based tests administered by study staff (One Step hCG Urine Pregnancy Test (UPT), Atlas Link Technology, Beijing) and positive UPTs were confirmed through repeat testing. ART regimen information, CD4 cell count and viral load data were collected at Baseline and during follow-up and confirmed through medical record review by the project coordinator and research assistants; pharmacy and laboratory records were used to adjudicate any data discrepancies.

2. Approach for Aim 1

2.1 Overview

We used group-based trajectory models to summarize longitudinal patterns of unmet need for contraception over the 12-month period. To identify factors associated with the developmental course of the outcome, we assigned women to trajectory groups using a maximum probability assignment rule and estimated predicted probabilities of trajectory group membership for individual-level characteristics measured at study entry. To assess model fit and to choose among the estimated trajectory models, we compared Bayesian Information Criterion (BIC) using Jeffreys's scale of evidence for Bayes factors.

2.2 Study Design

This is a secondary analysis of a previously conducted prospective cohort study, "Pregnancy Intentions and Incidence in HIV Positive Women on Antiretroviral Therapy in South Africa. All analyses were conducted among the 850 HIV-infected women who were previously on or being initiated onto ART during study enrollment. We defined the study origin as the date of original study enrollment, and baseline characteristics were assessed via interviewer-administered questionnaire. Follow-up began following study entry and concluded at the completion of 12 months. The primary outcome for Aim 1, unmet need for contraception, was assessed in monthly intervals beginning at enrollment and ending after the completion of 12 months of follow-up via 1) a short interviewer-administered questionnaire (behavioral variables) and 2) through linked clinical, laboratory and pharmacy records (clinical variables). We selected monthly intervals to minimize missing data (longer intervals, fewer measurements) while also minimizing the occurrence of conflicting, individual measurement within a given interval (shorter intervals, greater measurements).

2.3 Study Population

The study population included all 850 HIV-infected women who were previously on or being initiated onto ART originally enrolled in the parent study. Women were eligible at study

enrollment if they: were older than 18 but less than 35 years of age, not pregnant or breastfeeding, had not delivered a pregnancy in the previous three months, were taking ART, were sexually active within the past 12 months, had previously undergone a tubal ligation, hysterectomy, bi-lateral oophorectomy or were diagnosed as permanently infertile (Table 3.1).

2.4 Outcome Measures

The primary outcome for Aim 1 is unmet need for contraception, measured at repeat visits over 12 months of study follow-up. Our interest lies in assessing unmet need for safe and highly effective reliable contraception among HIV-infected women on ART in South Africa. To determine unmet need for contraception in our study, we adapted the unmet need for family planning algorithm proposed by Bradley et al. (2012) (Figure 3.1).[68] The algorithm was constructed to estimate unmet need for family planning using Demographic and Health Surveys (DHS) data, and accounts for multiple factors including fertility desires, contraceptive use, pregnancy status, fecundity and marital status. In our study, women were considered to have unmet need for contraception at a given study visit if they reported 1) being married, living with a partner, or being sexually active in the three months preceding study enrollment, 2) not currently trying to become pregnant, and 3) not reporting use of a reliable contraceptive method including oral contraceptives, injectables, a hormonal implant or an intrauterine device (Figure 3.2) As rates of unintended pregnancy are comparable among women who do not use family planning methods and among those who report condom use alone,[5,65] women who reported condom use as their primary method of family planning were not considered to be using a reliable method of contraception.

As a secondary outcome, we also assessed fertility intentions and contraceptive use measured at repeat visits over 12 months of study follow-up.

Measuring unmet need for contraception at study enrollment

Unmet need for contraception was calculated per the aforementioned algorithm using survey questions around fertility intentions and contraceptive use (Table 3.2). We adapted the

algorithm to include fertility intentions, as measures around fertility desires were not captured during study follow-up. Because a focus on married or in-union women misses the contraceptive practices and needs of sexually active women outside of these partnerships, we opted to calculate unmet need for contraception among all who were partnered or sexually active, irrespective of marital status.[68] Since pregnant and postpartum women were not eligible to participate, all women were classified as "not pregnant" at study entry (Table 3.1). As women who were knowingly infertile were also ineligible for study entry (Table 3.1), all women were considered fecund. All other women who intended to prevent or delay pregnancy at the time of study enrollment but were not using a reliable method of contraception were considered to have unmet need for contraception at enrollment.

Measuring unmet need for contraception during follow-up

During follow-up, time-updated measures of fertility intentions, contraceptive use and pregnancy status were re-entered into the algorithm to reflect changes in unmet need at each study visit (Table 3.2). Because pregnant women cannot experience the outcome of unmet need for contraception, women who became pregnant during follow-up were censored at incident pregnancy.

Measuring fertility intentions at baseline and during follow-up

Current fertility intentions were assessed at baseline and during follow-up using time-updated measures (Table 3.2).

2.5 Predictors

A variety of *a priori* specified baseline characteristics were evaluated as potential predictors of trajectory group membership. We selected predictors of interest from known clinical and behavioral factors associated with unmet need for contraception in HIV-infected women identified in a systematic review. Predictors identified in preliminary analyses included: demographic characteristics (age, relationship status), measures of wealth or socioeconomic status (education, income, recipient of a social grant), having prior children, partner desires

a/another child, measures or partner communication (disclosed HIV status to main partner, experienced physical intimate partner violence with main partner), measures of provider interaction (provider discussed options for future childbearing, provider discussed PMTCT, provider discouraged having more children, provider discussed hormonal contraception), HIV-related clinical outcomes (CD4 count, time on ART) and measures of hormonal contraception experience (experienced problems with current contraceptive method of choice, heard of any ART/contraceptive interaction). To avoid a potential lack of positivity during modeling, variables that informed our definition of unmet need for contraception were excluded from predictor analyses.

2.6 Analytic Plan for Aim 1

Modeling unmet need for contraception using group-based trajectory models

Group-based trajectory models are a class of finite mixture models designed to analyze data composed of a mixture of two or more groups whose outcomes are thought to be generated by distinct statistical processes.[31] These models assume that the population of interest comprises a mixture of subgroups that follow different developmental trajectories. Implicit in group-based trajectory modeling is the assumption that the true distribution of these subgroups across population members is unknown. As such, discrete trajectory groups are defined to approximate what is likely a continuous population distribution of trajectories of unknown shape. These groups can be thought of as latent longitudinal strata, and the shapes of the trajectories are described by a polynomial function of age or time.

Group-based trajectory models are data driven, meaning that only the study data are used to identify the number of groups that best fit the data and the shape of the trajectory for each group.[98] The data also provide an estimate of the proportion of the population whose measured behaviors “conforms most closely to each trajectory group”.[98] Figure 3.3 provides an overview of the general model and its key outputs.

Our model follows a binary logit distribution and estimates the probability that individual i at time t has an unmet need for contraception, conditional on membership in trajectory group j:

$$\alpha_{it}^{j} = \frac{e^{\beta_0^j + \beta_1^j X_{it} + \beta_2^j X_{it}^2 + \beta_3^j X_{it}^3}}{1 + e^{\beta_0^j + \beta_1^j X_{it} + \beta_2^j X_{it}^2 + \beta_3^j X_{it}^3}} \quad \text{(equation 1)}$$

where X is a variable representing age, time or visit number. For instances in which there are more than two trajectory groups (as was expected in our analysis), this model generalizes to a multinomial logit model.

In group-based trajectory models, parameter estimates are the product of maximum likelihood estimation, and as such are consistent and asymptotically normally distributed.[31,99-102] These parameters maximize the probability of Y_i, where Y_i denotes a longitudinal sequence of measurements from individual i over T time periods. If the parameters were constant across all individuals, the expected trajectory of all individuals would be identical. Since group-based trajectory models do not assume constancy, trajectories are summarized by a finite set of different polynomial functions with differing parameter estimates, where each function corresponds with a trajectory group, j. To define trajectories of unmet need for contraception over the study period, we used a binomial probability distribution to construct the likelihood function. Construction of the likelihood function requires the aggregation of the J conditional likelihood functions, $P^j(Y_i)$, to form the unconditional probability of the data, Y_i:

$$P(Y_i) = \sum_j^J \pi_j P^j(Y_i), \quad \text{(equation 2)}$$

where $P(Y_i)$ is the unconditional probability of observing individual i's longitudinal sequence of measurements, Y_i. It equals the sum across the J groups of the probability of Y_i, given i's membership in group j weighted by the probability of membership, π_j. Thus, the likelihood for

the entire study sample is the product of the individual likelihood functions for the N individuals that comprise the sample.

Model Estimation

We estimated models using Proc Traj, a free downloadable add-on package to base SAS (SAS, version 9.4, Cary, NC). Proc Traj uses a general quasi-Newton procedure to implement a search routine to locate the parameter estimates that maximize the likelihood function and has been shown to be superior for identifying underlying longitudinal trajectories relative to other methods.[103,104]

Model Selection

We used the Bayesian Information Criterion (BIC) to compare models with differing numbers of groups, with a smaller BIC corresponding to a better-fitting model.[105] The BIC is commonly used in the trajectory model literature, and assesses model fit by balancing model complexity versus goodness of fit to the sample data. The number of parameters is determined by the order of the polynomial (e.g., second order, third order) used to model each trajectory as well as the total number of groups. For a given model, BIC is calculated as:

$$BIC = log(L) - 0.5k\ log(N) \qquad \text{(equation 3)}$$

where L is the value of the model's maximum likelihood, N is the sample size of the study population, and k is the number of parameters in the model. The first component of the equation measures the improvement in model fit gained by generalizing the model to include additional parameters. The second component results in a penalty for the addition of more parameters. Thus, the addition of another trajectory group is only warranted if the change in $log(L)$ is larger than the penalty for adding additional parameters.

We employed a two-stage model selection process to select the number of groups to include in the final model. In the first stage we estimated one model for each possible value of J, from one group to a maximum of six groups as is consistent in the trajectory literature.[31] Each

model was compared with the same order polynomial (e.g. quadratic, cubic) and the number of groups in the final model determined for the value J with the highest BIC score. Once J was determined, the preferred order of the polynomial specifying the shape of each trajectory was selected (second stage). Quadratic and cubic specifications were compared using Jeffreys's scale of evidence for Bayes factors (Table 3.3).[105,106]

Calculating Posterior Probabilities of Group Membership

Posterior probabilities of group membership can be used as an additional method to assess model adequacy, and to assign behavioral profiles of trajectory group members. The posterior probability of group membership measures the probability that an individual, i, belongs to a specific trajectory group, j. Because the posterior probability of group membership cannot be calculated directly from the model's parameter estimates, posterior probabilities are calculated using Bayes's Theorem and weighted by the probability of group membership, $\hat{\pi}_j$. Individuals are then linked to a trajectory group using a maximum-probability assignment rule, which assigns individuals into a trajectory group to which their posterior probability is highest. Once individuals are assigned, we calculated the average posterior probability of group membership ($AvePP$), ensuring a mean $AvePP \geq 0.7$ for each trajectory group.

After individuals were assigned membership to a trajectory group, summary statistics for individual characteristics were calculated by group. These summaries create a profile of demographics and behavioral characteristics for the "average" group member,[98] providing early insight into factors associated with group membership.

Adding Covariates to the Model

Though calculation of posterior probabilities allowed us to construct profiles of trajectory group membership, these profiles are a collection of univariate contrasts that do not control for correlations among the predictors. They also do not provide a distinct mathematical relationship between the probability of group membership, π_j, and each of the variables of interest. Thus, to

formally assess predictors of trajectory group membership, we used an extension of the general model that allows the probability of trajectory group membership to depend on *a priori* specified behavioral characteristics (*see Predictors*).

We extended the general model (see *Modeling unmet need for contraception using group-based trajectory models*) so that the probability of group membership, π_j, was allowed to vary with individual characteristics:

$$\pi_j(x_i) = \frac{e^{x_i\theta_j}}{\sum_j e^{x_i\theta_j}} \qquad \text{(equation 4)}$$

where x_i is a vector of characteristics and θ_j are the estimated parameters that capture the conditional probability of group membership, $\pi_j(x_i)$, in a given group.[98]

We first constructed a multinomial outcome for group membership based on the number of groups identified by the final predictor-free model. We then assigned women to a specific trajectory group based on their maximum posterior membership probability. We then fit a multinomial regression model with this assigned trajectory group as the outcome and the predictors of interest as explanatory variables. Covariates were removed from the full model using a "backward" selection procedure.[107] Once a final set was identified, we re-estimated the trajectories jointly with the predictors. We included this second stage to ensure that our coefficients and standard errors properly accounted for covariance between parameter estimates and the probabilities of membership in each trajectory group. To determine how large an impact each characteristic has on the probability of group membership, and the extent to which these characteristics predict an individual's trajectory group membership, we calculated odds ratios and predicted probabilities using our optimal trajectory as the referent.

2.7 Power and Sample Size Considerations

All analyses for Aim 1 are descriptive, obviating the need for a formal power assessment. The key sample size questions for Aim 1 relate to precision and power to identify differences in trajectory groups. We anticipated that the repeat measurements collected among

the 850 women in our available sample were sufficient to yield precise estimates and to detect meaningful differences in trajectory group membership.

2.8 Missing Data

Complete case analysis may be valid if the amount of missingness is small (less than 10%).[108] For all predictors of interest, we elected to use complete case analysis as missing data accounted for less than 3% of observations. For missing values of unmet need for contraception, we re-estimated trajectories using quarterly intervals assessments (every three months). This approach minimized missing data resulting from our choice to finely measure unmet need for contraception every month.

2.9 Additional Analyses

This investigation primarily focused on characterizing trajectories of unmet need for contraception in a real-world population of HIV-infected women engaged in HIV care, and study enrollment was our origin for main analyses. In sub-analyses, we restricted trajectory models to women who had initiated ART within three months of study enrollment ("recent initiators") to better identify distinct trajectories of unmet need for contraception in the immediate period following ART initiation. Models were fit systematically using the same processes as described for the full cohort.

We hypothesize that contraceptive need, and by extension unmet need for contraception, varies over a short-term 12-month period. Central to this hypothesis is the notion that fertility intentions, contraceptive use, or both also vary over the study period. To evaluate the potential volatility of these measures, conducted an additional descriptive analysis to characterize potential differences in fertility intentions and contraceptive use by trajectory group over the study period. To do so, we used a maximum-probability assignment rule to assign women to the trajectory group for which they had the highest predicted posterior probability from the best fitting model.[31,102] We then descriptively examined the proportion of women trying to

conceive and the proportion of women using hormonal contraception within each interval, stratified by trajectory group.

Group-based trajectory models provide an empirical means of identifying groups or clusters of individuals following distinct developmental progressions over a given period.[31] In contrast, more standard statistical methods of longitudinal data analysis are designed to account for individual variability about a mean population trend.[102] To further assess the utility of the "finite mixture modeling" approach employed by group-based trajectory models in identifying heterogeneity, we simultaneously fit a log-binomial model for unmet need for contraception and generated prevalence estimates at repeat intervals over the study period. Results were visually presented and compared with results from the group-based trajectory models.

2.10 Sensitivity Analyses

Though a high proportion of women were retained through the end of the study period, we induced some missingness during follow-up visits by finely measuring unmet need for contraception every month. We did this to maximize the number of time points included in the group-based trajectory models so that we could infer granular changes in the predicted probability for unmet need for contraception over the entire study period. In sensitivity analyses for both the full cohort and recent initiators, we re-estimated trajectories using quarterly intervals assessments (every three months) to minimize missing data.

Unmet need for contraception was measured during routine HIV clinical care visits, and women who changed their fertility intentions following their previous care visit may have been misclassified as having unmet need for contraception. Specifically, women who became pregnant during follow-up may have changed their fertility intentions (from not trying to trying) prior to conceiving, but this change may not have been detected by our study's design as women were censored at pregnancy. To account for potential informative censoring at time of pregnancy resulting from this unmeasured change in fertility intentions, we repeated our main

analysis and restricted our cohort to those women who did not become pregnant during follow-up.

3. Approach for Aim 2

3.1 Overview

To better understand how childbearing decisions affect a woman's relationship with HIV care, we estimated the effect of fertility intentions on attendance at clinic visits over the 12-month study period. To estimate odds ratios for attendance at clinic visits, we fit a series of generalized linear models using generalized estimating equations (GEE) to account for repeat observations within women. We censored women at pregnancy. We adjusted models for a minimally sufficient set of confounders as identified by a directed acyclic graph (DAG), and explored potential effect measure modification (EMM) by select clinical characteristics identified *a priori*.

3.2 Study Design

This aim is a secondary analysis of a previously conducted prospective cohort study, "Pregnancy Intentions and Incidence in HIV Positive Women on Antiretroviral Therapy in South Africa". All analyses were conducted among the 850 HIV-infected women who were previously on or being initiated on ART during study enrollment. Our origin was defined as the date of original study enrollment, and characteristics were assessed at enrollment via interviewer-administered questionnaire. Follow-up began at study entry ("Month 0") and concluded at the completion of 12 months. The frequency of follow-up varied per woman depending on provider scheduling, clinic recommendations or provincial ART supply; however, women were recommended to attend HIV clinical care visits every three months, at minimum.[32]

3.3 Study Population

The study population included all 850 HIV-infected women who were previously on or being initiated onto ART originally enrolled in the parent study. Women were eligible at study enrollment if they: were older than 18 but less than 35 years of age, not pregnant or

breastfeeding, had not delivered a pregnancy in the previous three months, were taking ART, were sexually active within the past 12 months, had previously undergone a tubal ligation, hysterectomy, bi-lateral oophorectomy or were diagnosed as permanently infertile (Table 3.1).

3.4 Exposure Measures

The objective of this analysis was to determine if fertility intentions affect a woman's relationship with HIV care. **We hypothesized that women who intend to become pregnant would have a more consistent relationship with care compared to women who intend to prevent or delay pregnancy**. We considered fertility intentions our exposure of interest.

Time-fixed fertility intentions were assessed categorically at study enrollment as a measure of whether or not a woman was trying to conceive at time of interview (yes/no), trying to conceive in the next 12 months (yes/no/maybe), or trying to conceive at some point in the future (Table 3.2).

Time-varying fertility intentions were assessed dichotomously during follow-up (Table 3.2). Women were asked at each visit if they were currently trying to conceive (yes/no). We compared those women who were trying to conceive with those who were not at each visit.

3.5 Outcome Measures

The primary endpoint in this analysis is **attendance at clinic visits** over the 12-month period of observation. **Attendance at clinic visits** may be used as a measure of retention,[112] and indicates a period of interruption or engagement in HIV care for a given interval of time. The measure captures the number of "no show" visits during an observation period of interest. In our study, follow-up visits coincide with routine clinical care visits every 1-3 months based on clinic protocol, provider recommendations and provincial ART supply. Because date of next clinic visit was not routinely collected during the study period, a "days late" or traditional "missed appointments" definition of attrition is not feasible for our study; however, attendance within defined intervals or periods can be readily determined (Figure 3.4). As all women in this analysis

were on or being initiated onto ART, we measured attendance at clinic visits in repeat, discrete three-month intervals. A “no show” constituted a failure to return to clinic within a given interval. Because women may eventually return to care, multiple intervals of missed visits are possible over the course of the 12-month period. As our interest was in characterizing women with one or more missed visits over a short-term period, the primary endpoint of interest for this analysis was a dichotomized measure of whether or not a woman attended a visit within a given interval (yes/no), captured at repeat study visits over time. Administrative censoring occurred at the completion of 12 months, known transfer date, un-enrollment from the study, or date of death. Additionally, women who became pregnant during the study were referred to antenatal care (ANC), and censored date of confirmed pregnancy.

3.6 Confounders and Effect Measure Modifiers

We used covariate adjustment to balance the distribution of time-fixed characteristics captured at study enrollment for each exposure outcome relationship. A minimally sufficient set of covariates for adjustment was identified using a directed acyclic graph (DAG) (Figure 3.5):

Age: [30,113-115] Age at study entry

Time-on-ART:[114,116,117] Time spent on ART prior to study entry

Partner fertility intentions: Partner wants a/another child

Postpartum status: [9,11,115] End of last known pregnancy occurred ≤6 months prior to study entry

Prior children: [113,114,116,118] Number of children currently living

Provider discouraged childbearing: Provider discouraged having a/another child

Relationship status: [114,119] Married, living with a partner, widowed, separated or divorced

In preliminary analyses, no covariates were identified as potential time-varying confounders. We suspect this was because our exposure was not affected by HIV clinical outcomes (e.g., HIV-1 RNA viral load, CD4 cell count) in our assessment of the literature. Both pregnancy and

use of hormonal contraception were identified as intermediate factors on the causal pathway between each measure of fertility intentions and attendance at HIV clinical care visits (Figure 3.5). As our interest lies in estimating the total effect of fertility intentions on attendance, we opted not to formally control for pregnancy or contraceptive use in this analysis.

3.7 Analytic Plan for Aim 2

Overview of Analytic Approach

Percentages for discrete characteristics and medians and quartiles for continuous characteristics were calculated for women at study entry and stratified by dichotomous time-fixed fertility intentions (trying to conceive in the next 12 months vs. not) captured at enrollment. Fisher's exact test was used to compare the differences in proportions between arms for categorical variables, and Wilcoxon rank-sum tests were used to compare medians for continuous data (with alpha 0.05). To estimate the effect of fertility intentions on attendance at clinic visits, we used GEE with a logistic link to estimate odds ratios and predicted probabilities. We used a time-lag model to account for time-varying fertility intentions captured during follow-up.

Estimating the Effect of Time-Fixed Fertility Intentions on Attendance

We used GEE with a logistic link to estimate the effect of time-fixed fertility intentions captured at study enrollment on the odds of missing an HIV clinical care visit over the study period. We compared women who were trying to conceive (at study enrollment or in the next 12 months) with those that were not trying to conceive. Robust variance estimators with an exchangeable correlation matrix were used to account for within-subject correlation. We adjusted for the minimally sufficient set of confounders identified in DAG analyses.

Estimating the Effect of Time-Varying Fertility Intentions on Attendance

We similarly used GEE with a logistic link to estimate the effect of time-varying fertility intentions on the odds of missing an HIV clinical care visit over the study period. We compared women who were trying to conceive at each visit with those that were not. To ensure a woman's

fertility intentions preceded her attendance assessment for a given interval, we used the value of her fertility intentions from the preceding interval during modeling. To account for missing exposure data, we considered both complete case analysis and inverse probability weighting.

Assessing Effect Measure Modification

Since our study sample comprises women with a variety of ART experiences, we also assessed potential effect measure modification (EMM) by **time-on-ART, age** and **CD4 count**. For each potential modifier we dichotomized fertility intentions, comparing those women that were trying to conceive at enrollment with those that were not (current fertility intentions) and comparing women that had plans to conceive with those who had no plans to conceive (any fertility intentions).

To assess EMM by ART duration, we compared women who had initiated ART within three months of study enrollment (recent initiators) with those that had been on ART for more than three months (ART experienced). Our cutoff of three months was used to approximate those who had started ART on or around the time of study entry. Age was categorized about the median of 30 years and CD4 count was categorized about the common threshold of 200 cells/μl. To formally test for effect measure modification, we included an interaction term between each dichotomized exposure of fertility intentions and each of the proposed modifiers, where interaction terms with Wald test statistic p-values of <0.10 were considered significant. We considered both the magnitude and precision of stratum-specific estimates when making a final determination of EMM.

3.8 Power and Sample Size Considerations

We parameterized our power calculation for a simple logistic regression model, estimating the odds ratio for the association between current fertility intentions (dichotomized as trying to conceive vs. not trying to conceive) and attendance at HIV clinical care visits. As longitudinal, repeated measures typically allow for higher statistical power than cross-sectional designs, our power calculation represents a conservative estimate of the statistical power

afforded by our study. We assumed a two-sided test for the statistical significance of the likelihood ratio chi-square statistic at alpha=0.05 and a total sample size of 850. We assumed that 30% of women were trying to conceive at enrollment, and that the proportion of those not trying to conceive averaged 70% attendance at HIV clinical care visits, as estimated by external data that report high attendance at HIV clinical care visits 12 months after ART initiation.[120] Finally, we varied the expected odds ratios from 1.1 to 2.0 to cover a range of plausible effect estimates in the hypothesized direction. Figure 3.5 shows the power curve over the range of odds ratios above the null. Overall, for all odds ratios greater than 1.65 we maintained a statistical power above 80% to estimate the effect of fertility intentions on odds of attendance at HIV clinical care visits.

4. Tables and Figures

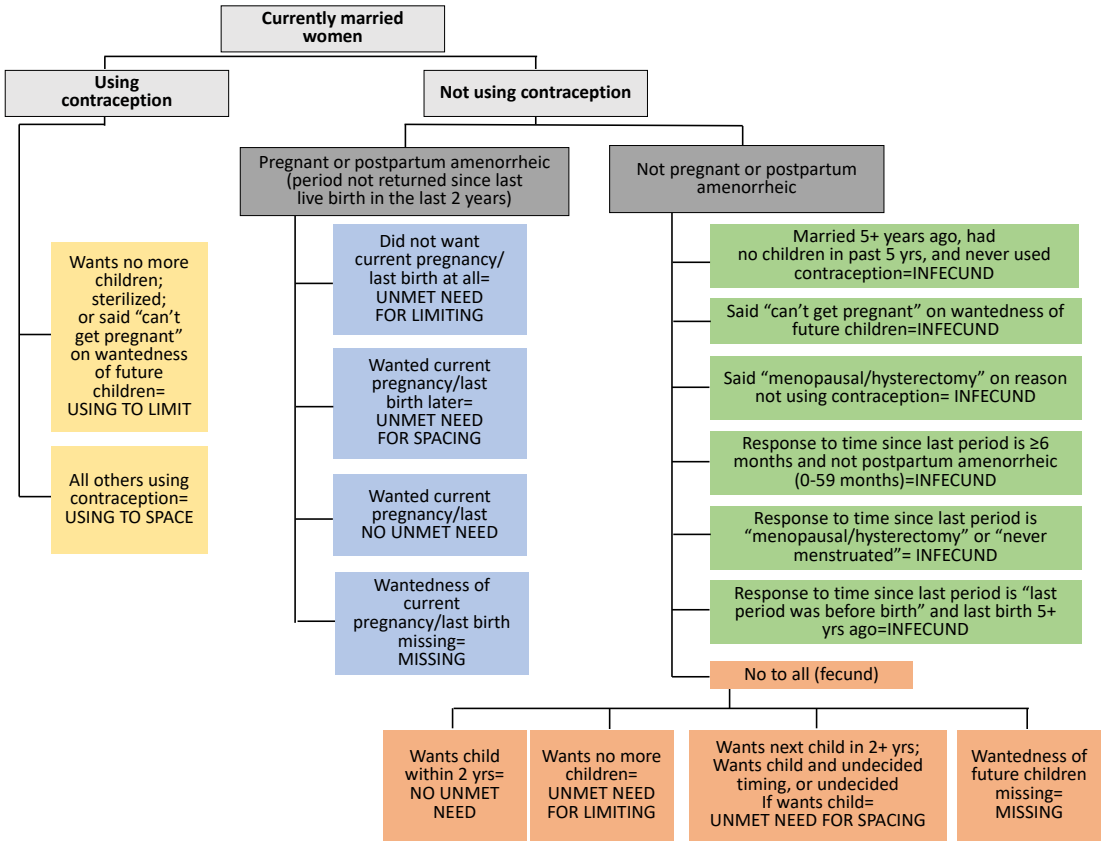
TABLE 3.1 Characteristics of parent study	
Objective	The objectives of the parent study were to: 1) Determine the incidence of pregnancy in HIV-infected women on antiretroviral therapy (ART) in South Africa; and 2) Assess contraceptive use and associations with unplanned pregnancy in this population.
Study Design	Prospective cohort study
Study Population	850 non-pregnant, HIV-infected women aged 18 to 35 enrolled on ART who initiated treatment with CD4 count ≤200 cells/μl or WHO clinical stage 4 diagnosis
Eligibility Criteria	Between 18 and 35 years of age (inclusive); Not pregnant at time of study enrollment; Had not delivered a pregnancy within the three months preceding study enrollment; Not breastfeeding; Enrolled on ART or initiated ART at study enrollment; Sexually active within the 12 months preceding study enrollment; No previous tubal ligation, hysterectomy, bi-lateral oophorectomy; Not diagnosed as permanently infertile.

TABLE 3.2 Assessment of characteristics used to calculate unmet need for contraception			
Characteristic	**Measure**	**Timing of Assessment**	
		Enrollment	Follow-up
Contraceptive Use			
Current Contraceptive Use	Currently using contraception for family planning. (yes/no)	X	
Current Contraceptive Method	Family planning method currently being used. *Enrollment:* Open-ended and categorized by interviewer *Follow-up*: Participant self-reported (Oral contraceptives/ Condom/ Injectable/ IUD/ Partner vasectomy)	X	X
Reliable Contraceptive Use (derived)	Currently using reliable contraceptive method for family planning (yes/no). Includes oral contraceptives, injectables, or intrauterine device	X	X
Fertility Intentions			
Fertility Intentions (current)	Currently trying to get pregnant (yes/no)	X	X
Fertility Intentions (future)	If not currently trying, planning to become pregnant in the next 12 months (yes/no)	X	
	If not currently trying or planning to become pregnant in the next 12 months, planning to become pregnant someday (yes/no)	X	

TABLE 3.3 Jeffreys's scale of evidence for Bayes factors	
Bayes factor	**Interpretation**
$\boldsymbol{\beta ij < 1/10}$	Strong evidence for model j
$\boldsymbol{1/10 < \beta ij < 1/3}$	Moderate evidence for model j
$\boldsymbol{1/3 < \beta ij < 1}$	Weak evidence for model j
$\boldsymbol{1 < \beta ij < 3}$	Weak evidence for model i
$\boldsymbol{3 < \beta ij < 10}$	Moderate evidence for model i
$\boldsymbol{\beta ij > 10}$	Strong evidence for model i

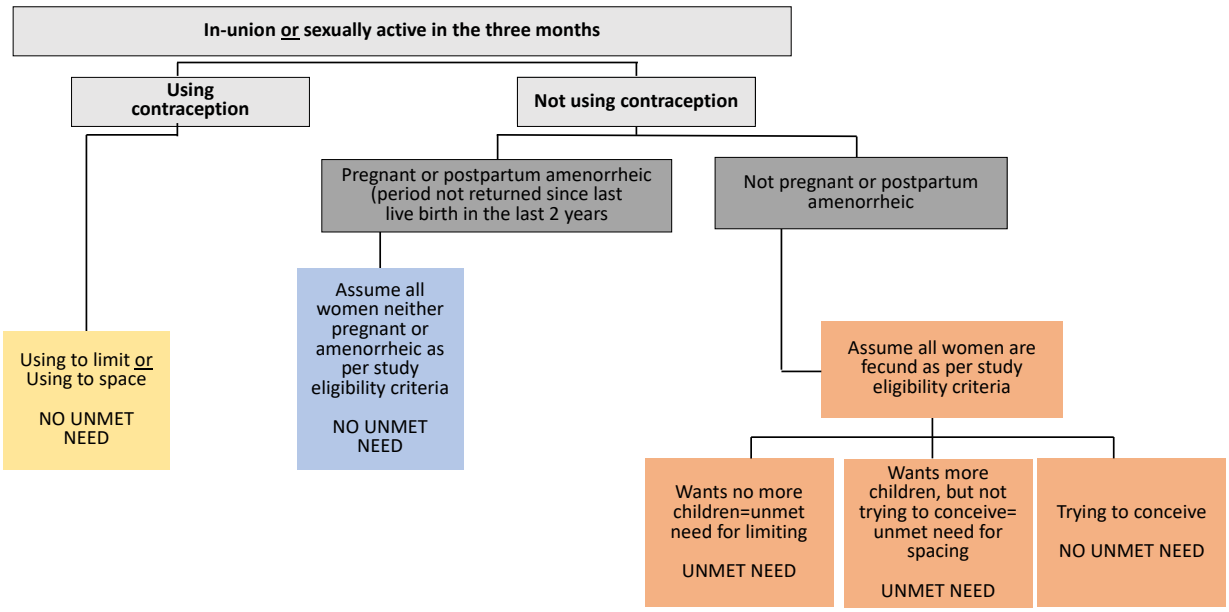
βij is the Bayes factor, and measures the posterior odds of i being the correct model given the data relative to j. βij is approximated as $e^{BIC_i - BIC_j}$. Adapted from Nagin, DS (2005).

FIGURE 3.1 Revised WHO algorithm to calculate unmet need for contraception



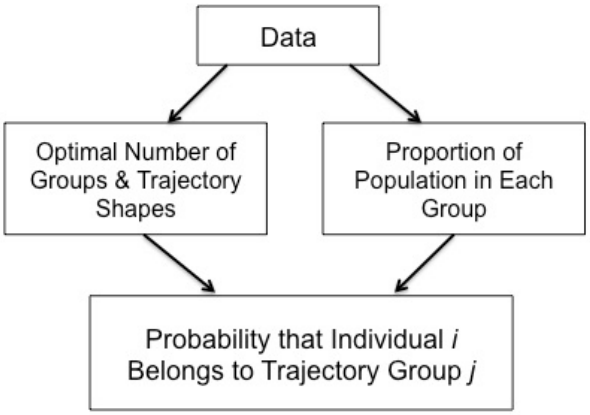
Adapted from Bradley, SEK et al. (2012).[68]

FIGURE 3.2 Modified WHO algorithm to calculate unmet need for contraception in this study



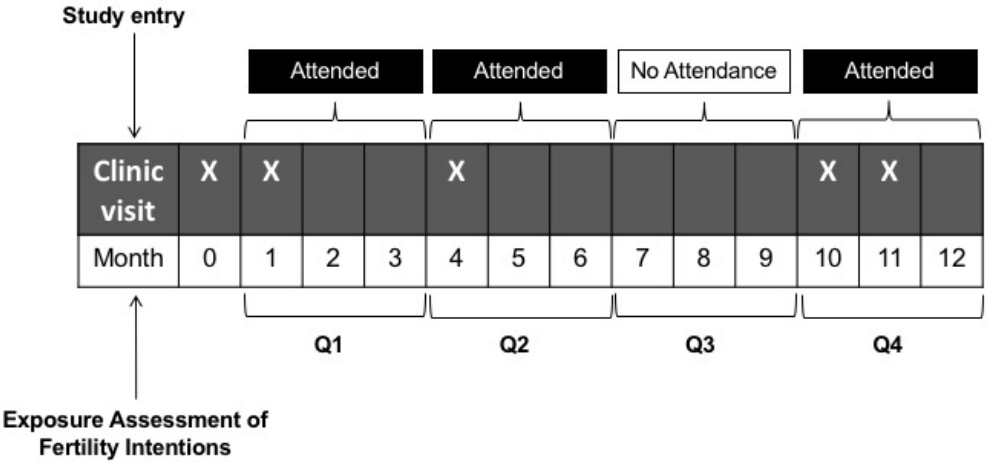
Adapted from Bradley, SEK et al. (2012).[68]

FIGURE 3.3 Overview of the group-based trajectory model



Adapted from Nagin, DS (1999).[98]

FIGURE 3.4 Attendance at HIV clinical care visits for a hypothetical patient



Note: An "x" denotes that the patient had a clinic visit in the corresponding month. A missed visit was defined as having no clinic visit in a three-month period. The first period (Q1) begins on the first day of the first month directly preceding study entry (Month 0). In this example, the patient had one clinic visit in the first period (Q1), one clinic visit in the second period (Q2), and one clinic visit in the second period (Q4). The patient did not attend in Q3 (adapted from Byrd KK et al., 2015)[121]

FIGURE 3.5 Directed acyclic graph (DAG) depicting the hypothesized relationship between fertility intentions and attendance at HIV clinical care visits

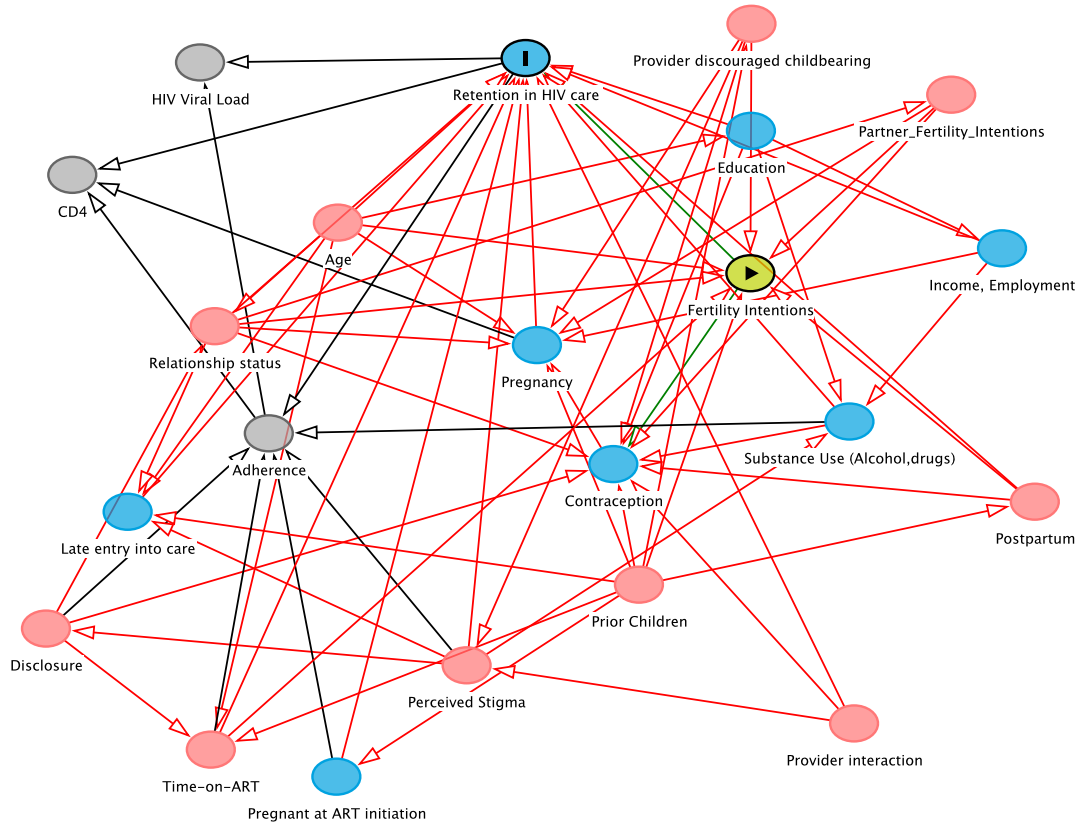
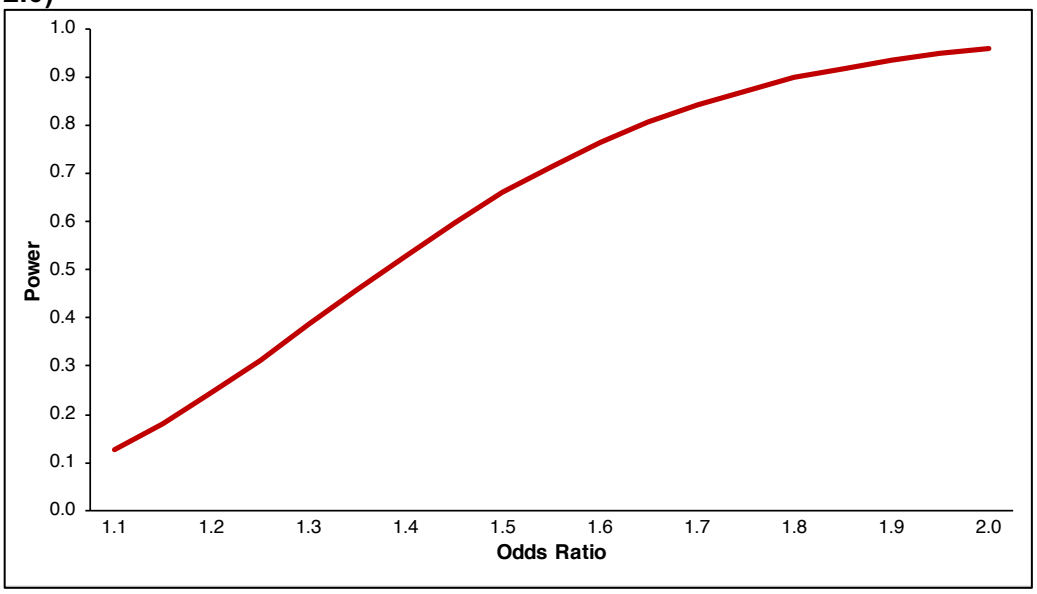


FIGURE 3.6 Expected statistical power to explore the association between fertility intentions and attendance at HIV clinical care visits over a range of odds ratios (1.1 to 2.0)



CHAPTER IV: AIM 1

Longitudinal patterns of unmet need for contraception among HIV-infected women on ART in Johannesburg, South Africa

1. Introduction

In HIV-infected women, prevention of unintended pregnancy through reliable contraceptive methods improves women's health and reduces both maternal and infant mortality.[1,2] Prevention of unintended pregnancy is also an effective strategy to reduce mother-to-child transmission,[3] and is the second prong of WHO's four-pronged framework for prevention of mother-to-child transmission (PMTCT).[4] For these reasons and to ensure women's reproductive rights, South African national contraception and family planning guidelines promote the availability of accessible and comprehensive contraceptive services to meet the family planning needs of women living with HIV.[5] In practice, however, HIV-infected women in South Africa still experience tremendous difficulties meeting their family planning needs.[6-9]

Family planning needs of HIV-infected women are likely to change over time, yet these changes may go undetected due to facility- and provider-level factors that preclude providers from routinely assessing fertility preferences and contraceptive use in the context of HIV clinical care. Comprehensive programs to reduce unmet need for contraception in HIV-infected women, broadly defined as a discrepancy between expressed fertility preferences and contraceptive use,[10] have traditionally focused on improving availability of services, increasing education and information dissemination around contraceptive use, and strengthening contraceptive counseling at the provider level.[7,11-14] However, even in settings where these enhanced family planning services are offered within HIV clinics, women may be reluctant to seek counseling[15]

and health-facility factors such as high patient volume and limited number of providers can affect patient-provider interaction time and quality of care. [16,17] To the extent that fertility intentions and contraceptive use are dynamic, this presents a missed opportunity for intervention.

Delineating patterns of unmet contraceptive need in HIV-infected women could help providers better understand the extent to which the risk for unintended pregnancy is likely to change over time. Furthermore, characterization of temporal trends or predictors of unmet need for contraception could inform more targeted screening practices within integrated reproductive health and antiretroviral therapy (ART) services, including both contraception provision and safer conception interventions. We assessed the longitudinal patterns of unmet need for contraception over a 12-month period within a cohort of HIV-infected women taking ART in South Africa.

2. Methods

2.1 Study Setting, Population and Design

Data were prospectively collected from four public-sector HIV outpatient clinics in inner city Johannesburg between 2009 and 2011 as part of a larger study to estimate the 12-month incidence of pregnancy in HIV-infected women on ART. Full study procedures and eligibility criteria have been previously described.[8,15,18] In brief, all HIV-infected, non-pregnant, sexually active women between the ages of 18-35 on or initiating ART were eligible for participation if they had not given birth in the last three months, were not breastfeeding, had not had a previous tubal ligation, hysterectomy, bi-lateral oophorectomy, and had not received a diagnosis of permanent infertility. Pregnancy was determined using urine-based tests administered by study staff (One Step hCG Urine Pregnancy Test, Atlas Link Technology, Beijing) and confirmed through repeat testing. ART regimen information, CD4 cell count and viral load data were confirmed through medical record review, pharmacy and laboratory records. After providing written informed consent, women meeting eligibility criteria completed an interviewer-

administered questionnaire to assess demographic and behavioral characteristics including fertility history and intentions, contraceptive use, and sexual risk behaviors.

2.2 Outcome Definition

Our outcome of interest was unmet need for contraception (yes/no), which we assessed at the time of each routine care visit according to an algorithm modified from that of Bradley et al.[19] Specifically, women were considered to have unmet need for contraception at a given study visit if they reported 1) being married, living with a partner, or being sexually active in the three months preceding study enrollment; 2) not currently trying to become pregnant; and 3) not currently using oral contraceptives, injectable, a hormonal implant or an intrauterine device. Women who met the first two criteria and reported condom use as their primary family planning method were considered to have unmet need, as rates of unintended pregnancy are comparable among women who do not use family planning methods and among those who report condom use alone.[8,20]

We assessed unmet need for contraception at monthly intervals after enrollment, corresponding to the routine care visits, for a total of 12-time points. In cases where a woman had two routine care visits within a given month, we employed a two-stage process for measurement selection. If another visit occurred in the subsequent interval, we retained only the first measurement for the month in question. If, however, no visit occurred in the next interval, we retained both measurements for the month in question provided they occurred at least 21 days apart, and assigned the second value forward to the next interval. This process accounted for the heterogeneity in clinic visit frequency among women, minimized missing data, and reflected any conflicting, individual measurement within a given interval. Women were censored at pregnancy, loss to follow-up, death, or the completion of 12 months of follow-up.

The original study protocol was approved by the University of the Witwatersrand Human Research Ethics Committee, Johannesburg, South Africa. Written informed consent was

obtained from all participants. The University of North Carolina at Chapel Hill Institutional Review Board also approved the secondary analysis presented here.

2.3 Statistical Analysis

We used group-based trajectory modeling to identify distinct longitudinal patterns of unmet need for contraception over the 12-month period.[21,22] Group-based trajectory modeling is an application of finite mixture modeling designed to identify clusters of individuals who follow a similar trajectory for a given outcome over time.[22] We first fit a series of predictor-free trajectory models to identify the optimal number of trajectories describing the population patterns of unmet need for contraception, fitting models with 2, 3, 4, or 5 trajectory groups to allow for heterogeneity while ensuring interpretability. Given the dichotomous nature of the outcome, we specified a logit link and binomial distribution, and we decided *a priori* to consider both quadratic and cubic specifications of each model to enable flexible trajectory shapes. We chose the optimal model based on optimum Bayesian information criterion (BIC) using Jeffreys's scale of evidence for Bayes factors.[23,24]

As unmet need for contraception is a function of both fertility intentions and contraceptive use, changes in unmet need may reflect changes in fertility intentions, contraceptive use, or both. Therefore, to delineate changes in the separate phenomena contributing to the composite outcome of unmet need for contraception, we conducted a descriptive analysis in which we graphically characterized both fertility intentions and contraceptive use over the study period. At each interval we assigned women to one of four mutually exclusive categories:1) those who had unmet need according to the definition above; 2) those who were married, living with a partner, or sexually active and using a reliable method of contraception to prevent pregnancy; 3) those who were married, living with a partner, or sexually active and trying to conceive, and 4) those who were not married, living with a partner, or sexually active. We conducted this descriptive analysis overall and by trajectory group (assigned on the basis of the maximum posterior probability of group membership [21,22]).

To identify predictors of trajectory group membership, we first constructed a categorical outcome for group membership based on the final predictor-free model, assigning each woman to a group based on her maximum posterior membership probability in each model.[21,22] We then fit a multinomial regression model with this assigned trajectory group as the outcome and the predictors of interest as explanatory variables. Predictors of interest were clinical and behavioral factors associated with unmet need for contraception in HIV-infected women as identified through a literature review. All predictors of interest were assessed at enrollment and are included in Tables 4.4 and 4.5. Predictors included demographics, measures of fertility history, partner-associated characteristics, measures of patient/provider interaction and HIV-related clinical outcomes.

In a second stage of the predictor analysis, we constructed a new group-based trajectory model for unmet need for contraception, retaining all predictors that were found to be significant (α=0.1) for at least one trajectory group comparison in the first stage.[21] We included this second stage to ensure that our coefficients and standard errors properly accounted for covariance between parameter estimates and the probabilities of membership in each trajectory group.[21]

We conducted all analyses in the full cohort and repeated them in a subgroup of women initiating ART within 3 months of enrollment, given the likelihood that fertility intentions may change rapidly immediately after ART initiation [25-27], as well as the distinctness of ART initiation as a clearly identifiable developmental origin and intervention point. In sensitivity analyses for both the full cohort and recent initiators, we re-estimated trajectories using quarterly interval assessments (every three months). All models were fit using Proc Traj (https://www.andrew.cmu.edu/user/bjones/index.htm) a free downloadable SAS add-on package (SAS, version 9.4, Cary, NC).

3. Results

3.1 Study Population and Follow-Up

A total of 850 women were enrolled and followed for up to 12 months. Over the 12-

month period, 149 women (17.5%) became pregnant and contributed a median of 6.2 months (IQR 4, 9) of follow-up before they were censored at time of pregnancy. Among the 701 women who did not become pregnant, median follow-up time was 11.4 months (IQR 9, 12), with 28 (4.0%) not returning to care after their initial study visit. Median time between follow-up visits was 1.7 months (IQR 1, 2) for women who became pregnant and 1.8 months (IQR 1, 2) for those who did not. No deaths were reported over the study period.

Women were on average 30 years of age (IQR 27, 33), and the majority were in a relationship (789/850, 92.8%) (Table 4.1). Most women (760/850, 89.4%) had previously been pregnant, with a median time since last pregnancy of 48 months (IQR 20, 96). The median time since HIV diagnosis was 24 months (IQR 12, 48), and median time since ART initiation was 13 months (IQR 5, 24).

Of the 850 women in the full cohort, 157 (18.5%) had initiated ART within three months of study enrollment ("recent initiators") and 693 (81.5%) had initiated ART more than three months prior to study enrollment ("ART experienced"). Demographics, behavioral characteristics and clinical characteristics differed by ART experience. Compared to ART-experienced women, a larger proportion of recent initiators reported at enrollment that they planned to become pregnant in the next 12 months (97/157 (61.8%) vs. 299/693 (43.2%)) and a smaller proportion were using hormonal contraception (21/157 (13.4%) vs. 203/693 (29.3%)) to prevent pregnancy.

Unmet need was assessed at study enrollment in both the full cohort and in recent ART initiators. Of the 850 women included in the full cohort, 469 (55.2%) had unmet need. The proportion of women with unmet need was similar among recent initiators of ART compared to women who were ART experienced (54.1% vs. 59.9%).

3.2 Longitudinal Assessment of Unmet Need for Contraception

A four-group quadratic model was selected as the optimal predictor-free model to identify patterns of unmet need over 12 months (Figure 4.1a). Half (50.0%) of the cohort was predicted to have a consistently high probability of unmet need (predicted probability of unmet

need between 79.0% and 98.0%) over the study period. Nearly a quarter (22.9%) were predicted to have a consistently low probability of unmet need (1.2%-8.0% probability of unmet need over time). Additionally, 16.7% had a steadily decreasing probability of unmet need (from 86.9% at month 0 to 3.1% at month 9) and 10.4% exhibited a sharp increase in this probability (from 6.0% at month 0 to 81.4% at month 12). Based on these trends for unmet need, we qualitatively described these groups as “consistently high,” “consistently low,” “decreasing,” and “increasing,” respectively.

In the sub-analysis of recent ART initiators (n=157), a four-group, predictor-free cubic model was selected to identify patterns of unmet need (Figure 4.1b). Similar to the model selected for the full cohort, nearly half (40.8%) of recent initiators were predicted to have a consistently high probability of unmet need (predicted probability of unmet need between 91.1% and 96.9% throughout). Women who were predicted to have a consistently low probability of unmet need (between 0.0% and 14.6% across the 12 months) accounted for 24.4% of recent initiators. Nearly a quarter (17.5%) of recent initiators were predicted to have a slowly increasing probability of unmet need (from 25.1% at month 3 to 94.5% at month 12), and a nearly identical proportion (17.4%) were predicted to have a decreasing probability of unmet need (from 88.3% at month 1 to 16.9% at month 9).

In sensitivity analyses where we re-estimated trajectories using quarterly intervals assessments, results were generally similar (Figure 4.3). Results were also similar in sensitivity analyses where we excluded women who became pregnant during follow-up (Figure 4.4)

3.3 Fertility Intentions and Contraceptive Use Over Time

Temporal patterns in the two distinct contributors to unmet need – fertility intentions and contraceptive use – varied dramatically across trajectory groups (Figure 4.2). In those who followed an increasing trajectory of unmet need (based on assignment to the increasing group using a maximum posterior membership probability), the proportion trying to conceive decreased over time (from 35.6% in month 0 to 10.3%% in month 12), as did the proportion

using reliable contraception to prevent pregnancy (from 61.6% in month 0 to 13.8% in month 12). In those who followed a decreasing trajectory of unmet need, the proportion trying to conceive increased over time (between 3.5% at month 0 and 45.5% at month 12) and the proportion using reliable contraception to prevent pregnancy also increased (between 4.3% and 16.9% over the 12 months). For women who followed trajectories of unmet need that were relatively constant (i.e. consistently low and consistently high), we observed little change in fertility intentions and contraceptive use over the 12 months. Results were similar in recent initiators.

3.4 Predictors of Trajectory Group Membership

Our multinomial logistic regression analysis allowed comparison of predictors for each of the four trajectory groups relative to each other group (i.e., sixteen possible comparisons). For simplicity, we focus here on the two main comparisons of greatest apparent clinical relevance. Specifically, based on our observation of similar "starting points" for the consistently high and decreasing trajectories (and for the consistently low and increasing trajectories), we describe predictors associated with membership in the decreasing group (compared to the consistently high group) and those associated with membership in the increasing group (compared to the consistently low group), as found using the two-stage process outlined above. Compared to the consistently high unmet need group, those in the decreasing group were likely to have fewer children (OR 0.4, 95% CI 0.3, 0.5) for each one-unit increase in number of living children) and were more likely to have a partner that desired a/another child (OR 4.2 95% CI 1.6, 10.9) (Table 4.2). Compared to the consistently low group, women in the increasing group were more likely to have reported a problem with their contraceptive method (OR 3.0, 95% CI 1.4, 6.6) (Table 4.3).

In analyses confined to recent initiators, we were unable to identify meaningful predictors of group membership in stage one due to the limited number of women assigned to each trajectory group, and models did not converge in stage two. Additional descriptive profiles of

trajectory group membership for both the full cohort and recent initiators are reported in Tables 4.4 and 4.5.

4. Discussion

Changes in fertility intentions following ART initiation, coupled with improvements in fecundity[20,28] and renewed sexual desire and greater coital frequency[25] are thought to contribute to increasing incidence of pregnancies in HIV-infected women after starting ART in the absence of compensatory contraceptive use. In this study, we demonstrated that HIV-infected women on ART in South Africa have a high probability of unmet need for contraception, and that rapidly changing fertility intentions and decisions about contraceptive use contribute to changing unmet need in a non-trivial subset of women.

Half of women in our full cohort were predicted to have a consistently high probability of unmet need that persisted over time. Approximately one in ten women in our full cohort and almost 20% of those recently initiating ART were predicted to have unmet contraceptive need that increased over time, indicating they were at higher risk of unintended pregnancy as time under observation increased. Notably, among women with increasing unmet contraceptive need, few were observed to have unmet need at study enrollment (Figure 4.4). Our findings are compatible with previous research showing a single assessment of contraceptive need is insufficient in identifying those at high risk for unintended pregnancy, even within a 12-month period.[8]

Consistent with other estimates of contraceptive use in South Africa, few women in our study were using a reliable method of contraception to prevent pregnancy at enrollment. Low uptake of hormonal contraception may reflect fear of side effects or health risks (e.g., heavy menstrual bleeding, irregular bleeding, bleeding between periods, lower abdominal pain), which are strongly associated with contraceptive discontinuation or switching in HIV-infected women in multiple studies.[29,30,31] Compared to women in our study who followed a trajectory of consistently low unmet contraceptive need, those with increasing unmet need were significantly

more likely to report problems or side effects with their method of contraception. Furthermore, a significant proportion of those who followed an increasing trajectory of unmet need discontinued their method of contraception over the 12-month period without a corresponding change in fertility intentions.

Changes in unmet need for contraception also reflect changes in fertility intentions. We found that among women with a decreasing unmet need for contraception over follow-up, the primary driver of reduced unmet need was increasing fertility intentions, not an increase in uptake of contraception. Previous studies have found that fertility intentions increase rapidly in the period following ART initiation,[25-27] though evidence is limited. Increasing fertility intentions among women on ART may also reflect partner fertility desires, and we found that women with a decreasing unmet contraceptive need were more likely to report a partner that desired a/another child. To the extent that fertility intentions reflect decisions around childbearing in both partners, comprehensive screening of family planning needs including asking women about their partner's fertility intentions, may offer additional opportunities to identify women who require safer conception counseling.

We observed that family planning needs of HIV-infected women changed frequently over time in this South African setting, yet in clinical practice fertility intentions and contraceptive use were infrequently assessed. While current national service delivery guidelines promote the integration of sexual and reproductive health services with HIV prevention, care and treatment in South Africa,[5] implementation of these guidelines in clinical practice has been limited.[32,33] Routine HIV clinical care visits represent a potential opportunity to regularly assess family planning needs, particularly among women on ART who may be unaware that their fertility will increase once started on ART. [20,28,34] Furthermore, regularly assessing the family planning needs of women who have trouble achieving viral suppression is critical for both prevention of horizontal transmission to HIV-uninfected partners and PMTCT. Our findings suggest that programs that include comprehensive screening for fertility intentions (for women and men),

increase patient and provider awareness about contraceptive side effects and alternative method options, and provide high-quality provider training on contraceptive methods and safer conception will be most effective in decreasing unmet need for contraception in HIV-infected women.

Our study is not without limitations. First, nearly half of women in this analysis reported condoms as their primary method of family planning at enrollment but were considered to have unmet need for contraception. As some of these women may have used condoms consistently and correctly, we may have overestimated the total number of women in our cohort with unmet need. However, women in this study who reported using condoms had nearly identical pregnancy rates as women who reported using no contraceptive method,[8] suggesting that the majority of women using condoms were not doing so effectively enough to prevent pregnancy. Second, all behavioral outcomes were measured by self-report and are subject to potential misclassification; however, questionnaires were administered in private by trained study staff who developed a strong rapport with the participants to minimize social desirability bias. Third, an emerging body of evidence suggests that binary measures of fertility intentions are insufficient to capture ambivalence around childbearing,[35,36] and we may have overestimated unmet need in some women who indicated they were not trying to become pregnant at a given study visit.[10] Fourth, data included in this study predate South African national service delivery guidelines for integrated family planning and HIV care and earlier thresholds for treatment initiation. At the time of study enrollment, non-pregnant women were only eligible for lifelong ART initiation with a CD4 count ≤200 cells/μl or WHO clinical stage 4 diagnosis, and trajectories of unmet need and predictors thereof may differ in the current era. However, we saw very little difference in CD4 count by trajectory group. Furthermore, trajectories were largely similar among recent ART initiators who started treatment for their own health.

We have shown that the family planning needs of HIV-infected women may change rapidly, driving dynamic trajectories of unmet need for contraception even over a 12-month

period. As more and more women initiate ART through South Africa's universal testing and treatment inititiative,[37] routine screening of fertility intentions combined with rapid service referral for reliable contraception and safer conception methods will be critical in ensuring that HIV-infected women are able to meet their reproductive needs.

5. Tables and Figures

TABLE 4.1 Characteristics at enrollment of 850 HIV-infected women taking ART in Johannesburg by ART initiation status, 2009-2011

	Overall N=850		ART Experienced* N=693		Recent ART Initiators† N=157	
	Median	IQR	Median	IQR	Median	IQR
Age (years)	30.4	27-33	30.5	28-33	30.0	26-32
Monthly income (ZAR)	2000.0	1000-3480	2000.0	1000-3500	1700.0	1000-3000
No. living children	1.0	1-2	1.0	1-2	1.0	0-2
Months since last pregnancy	48.0	20-96	48.0	18-84	72.0	26-96
Months since HIV diagnosis	24.0	12-48	28.0	15-48	11.0	3-24
CD4 count at enrollment (cells/µl)	312.0	178-462	356.0	242-510	149.0	87-179
Months on ART	13.0	5-24	16.0	9-29	1.0	0-2
	n	**%**	**n**	**%**	**n**	**%**
Education completed						
None-Grade 10	55	6.5	44	6.4	11	7.0
Grade 11-Grade 12	671	78.9	542	78.2	129	82.2
Post-grad degree or certificate	124	14.6	107	15.4	17	10.8
Employed	510	60.0	427	61.6	83	52.9
Married/cohabitating with a partner	378	44.5	300	43.3	78	49.7
In a relationship	789	92.8	655	94.5	134	85.4
Sexually active, last three months	754	89.4	627	91.0	127	82.5
Partner HIV status‡						
Negative	200	25.3	165	25.2	35	25.7
Positive	312	39.4	260	39.7	52	38.2
Unknown	279	35.3	230	35.1	49	36.0
Ever pregnant	760	89.4	630	90.9	130	82.8
Pregnant at HIV diagnosis	271	31.9	248	35.8	23	14.7
Pregnant at or after HIV diagnosis	380	44.7	347	50.1	33	21.0
Trying to conceive, currently	105	12.4	83	12.0	22	14.0
Trying to conceive, next year	396	46.6	299	43.2	97	61.8
Taking hormonal contraception	224	26.4	203	29.3	21	13.4
Using condoms for family planning	410	48.2	325	46.9	85	54.1

Abbreviations; IQR: Interquartile Range, ART: Antiretroviral therapy

* On ART >3 months at study entry

† Initiated ART within three months of study entry

‡ n=791

TABLE 4.2 Odds Ratios (95% Confidence Intervals) associated with membership in the "Decreasing" unmet need trajectory group (N=850)

	OR (95% CI)			
Characteristic	**Consistently High**	**Decreasing**	**Increasing**	**Consistently Low**
Number of living children*	**1**	0.4 (0.3, 0.5)	0.6 (0.4, 0.9)	0.6 (0.4, 0.7)
Employed	**1**	1.7 (0.9, 3.0)	1.9 (0.8, 4.4)	1.5 (0.9, 2.7)
Main partner desires a/another child	**1**	4.2 (1.6, 10.9)	0.5 (0.1, 2.9)	0.8 (0.5, 1.2)
Problems with contraceptive method	**1**	0.7 (0.3, 1.4)	1.9 (1.0, 3.7)	0.7 (0.4, 1.3)

Abbreviations; OR: Odds Ratio, CI: Confidence Interval
* Per one-unit increase in number of children

TABLE 4.3 Odds Ratios (95% Confidence Intervals) associated with membership in the "Increasing" unmet need trajectory group (N=850)

	OR (95% CI)			
Characteristic	**Consistently Low**	**Increasing**	**Decreasing**	**Consistently High**
Number of living children*	**1**	1.2 (0.8, 1.9)	0.7 (0.5, 1.0)	2.9 (1.5, 2.6)
Employed	**1**	1.1 (0.6, 2.2)	2.1 (1.2, 3.8)	1.2 (0.8, 1.8)
Main partner desires a/another child	**1**	1.3 (0.5, 3.4)	2.0 (0.8, 4.9)	0.6 (0.3, 1.0)
Problems with contraceptive method	**1**	3.0 (1.4, 6.6)	1.2 (0.5, 2.8)	1.3 (0.7, 2.4)

Abbreviations; OR: Odds Ratio, CI: Confidence Interval
* Per one-unit increase in number of children

TABLE 4.4 Characteristics of women assigned to "Consistently Low," "Increasing," "Decreasing," and "Consistently High" unmet need trajectory groups using a maximum-probability assignment rule (N=850)

	"Consistently Low" N=214 (25.2%)		"Increasing" N=73 (8.6%)		"Decreasing" N=116 (13.6%)		"Consistently High" N=447 (52.6%)	
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Posterior probability of group membership	0.95	0.71-0.99	1.00	0.89-0.72	0.99	0.85-1.00	0.90	0.70-0.98
Age (years)	30.1	27-32	29.8	28-32	30.3	27-33	30.8	27-33
Income (ZAR)	2000.0	1000-3000	2500.0	1700-4200	2000.0	1005-3200	2000.0	1000-3500
No. living children	1	0-2	1	0-2	1	0-1	1	1-2
CD4 count (cells/μl)	314.0	192-474	311.0	172-492	247.5	175-455	319.0	175-454
Months on ART	13.6	6-26	12.6	6-22	11.3	3-21	13.3	6-26
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Lost to follow-up at 6 months	20	9.4	1	1.4	4	3.5	35	7.8
Became pregnant during follow-up	35	16.4	6	8.2	17	14.7	91	20.4
Unmet need at study enrollment	12	5.6	4	5.5	107	92.2	346	77.4
Planned to conceive next 12 months	109	50.9	40	54.8	76	65.5	148	33.1
In relationship with main partner ≥3 years	108	50.5	50	68.5	68	58.6	290	64.9
Has living children	158	73.8	52	71.2	77	66.4	379	84.8
Education completed								
None-Grade 10	58	27.1	17	23.3	33	28.5	110	24.6
Grade 11-Grade 12	125	58.4	49	67.1	63	54.3	275	61.5
Post-grad degree or certificate	31	14.5	7	9.6	20	17.2	62	13.9
Social grant recipient	60	28.0	19	26.0	15	12.9	110	24.6
Employed	115	53.7	44	60.3	79	68.1	272	60.9
Disclosed HIV status to main partner*	145	83.8	55	75.3	27	75.7	356	82.4
Any physical IPV with main partner†	18	10.5	7	9.6	9	8.2	39	9.1

Main partner desires a/another child*	145	67.8	63	86.3	104	89.7	332	74.3
No	28	16.2	10	13.7	7	6.3	100	23.2
Yes	131	75.7	59	80.8	92	82.3	287	66.4
Unsure	14	8.1	4	5.5	12	10.8	45	10.4
Problems with prior contraceptive method	29	13.6	19	26.0	14	12.1	84	18.8
Provider discussed future childbearing	89	41.6	33	45.2	45	38.8	178	39.8
Provider discussed PMTCT	139	65.0	52	71.2	43	62.9	309	69.1
Provider discussed HC options	101	47.2	40	54.8	38	32.8	231	51.7
Provider discouraged having a/another child	9	4.2	7	9.6	5	4.3	32	7.2

Abbreviations; IQR: Interquartile Range, ART: Antiretroviral therapy, No.: Number, IPV: Intimate Partner Violence, HC: Hormonal Contraception, PMTCT: Prevention of Mother-to-child Transmission

* n=789

† n=784

TABLE 4.5 Characteristics of recent ART initiators assigned to "Consistently Low," "Increasing," "Decreasing," and "Consistently High" unmet need trajectory groups using a maximum-probability assignment rule (N=157)

	"Consistently Low" N=41 (26.1%)		"Increasing" N=24 (15.3%)		"Decreasing" N=21 (13.4%)		"Consistently High" N=71 (45.2%)	
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Posterior probability of group membership	0.95	0.71-0.99	1.00	0.89-0.72	0.99	0.85-1.00	0.90	0.70-0.98
Age (years)	28.8	27-31	30.6	25-33	30.3	28-33	30.0	27-32
Income (ZAR)	1300.00	500-2000	2500.0	850-3500	1800.0	1000-4200	1800.0	1300-3000
No. living children	0	0-1	1	0-1	1	0-1	1	0-2
CD4 count (cells/μl)	132.0	71-192	165.0	110-179	151.0	105-186	140.0	68-175
Months on ART	1.9	1-2	0.7	0-2	0.9	0-2	1.0	0-2
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Lost to follow-up at 6 months	4	9.8	1	4.2	1	4.8	7	9.9
Became pregnant during follow-up	9	22.0	2	8.3	0	0	14	19.7
Unmet need at study enrollment	1	2.4	11	45.8	18	85.7	64	90.1
Planned to conceive next 12 months	22	53.7	20	83.3	18	85.7	30	42.3
In relationship with main partner ≥3 years	8	19.5	14	58.3	13	61.9	44	62.0
Education completed								
None-Grade 10	15	36.6	8	33.3	7	33.3	26	36.6
Grade 11-Grade 12	24	58.5	11	45.8	12	57.1	38	53.5
Post-grad degree or certificate	2	4.9	5	20.8	2	9.5	7	9.9
Social grant recipient	6	14.6	4	16.7	1	4.8	12	16.9
Employed	17	41.5	12	50.0	12	57.1	42	59.2
Disclosed HIV status to main partner*	21	84.0	16	69.6	18	85.7	57	87.7
Any physical IPV with main partner†	2	8.3	0	0	3	14.3	10	15.4

Main partner desires a/another child*								
No	2	8.0	0	0	1	4.8	13	20.0
Yes	22	88.0	21	91.3	18	85.7	44	67.7
Unsure	1	4.0	2	8.7	2	9.5	8	12.3
Problems with prior contraceptive method	1	2.4	4	16.7	3	14.3	11	15.5
Provider discussed future childbearing	18	43.9	8	33.3	7	33.3	35	49.3
Provider discussed PMTCT	21	51.2	14	58.3	11	52.4	39	54.9
Provider discussed HC options	12	29.3	10	41.7	6	28.6	26	36.6
Provider discouraged having a/another child	5	12.2	1	4.2	1	4.8	1	1.4

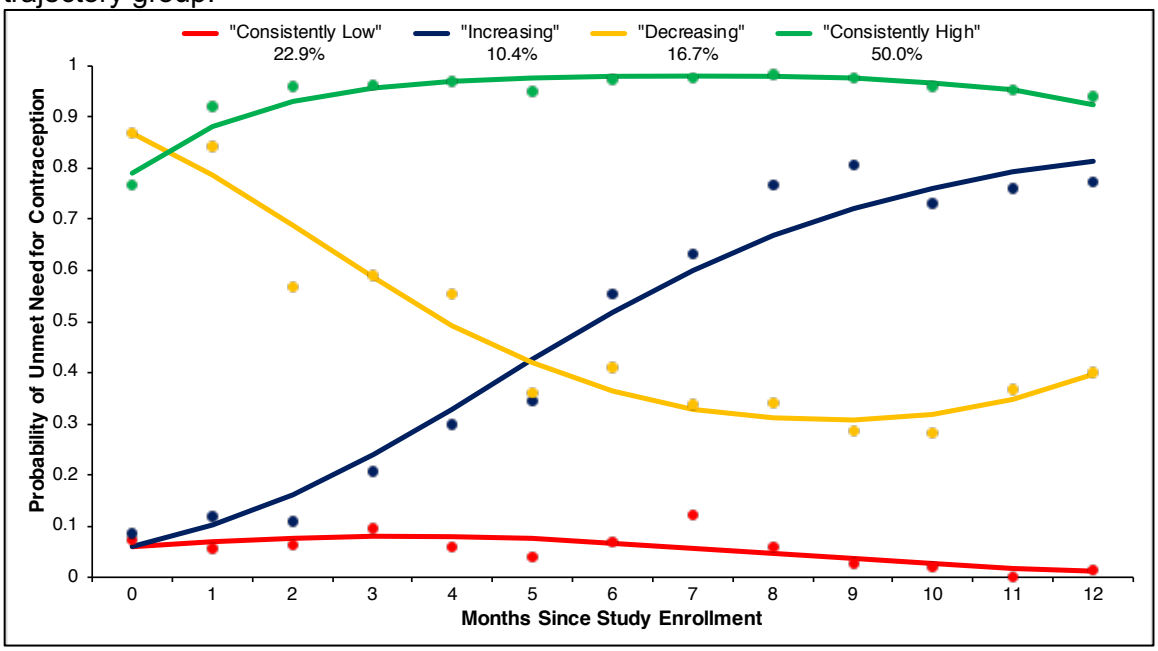
Abbreviations; IQR: Interquartile Range, ART: Antiretroviral therapy, No.: Number, IPV: Intimate Partner Violence, HC: Hormonal Contraception, PMTCT: Prevention of Mother-to-child Transmission

* n=134

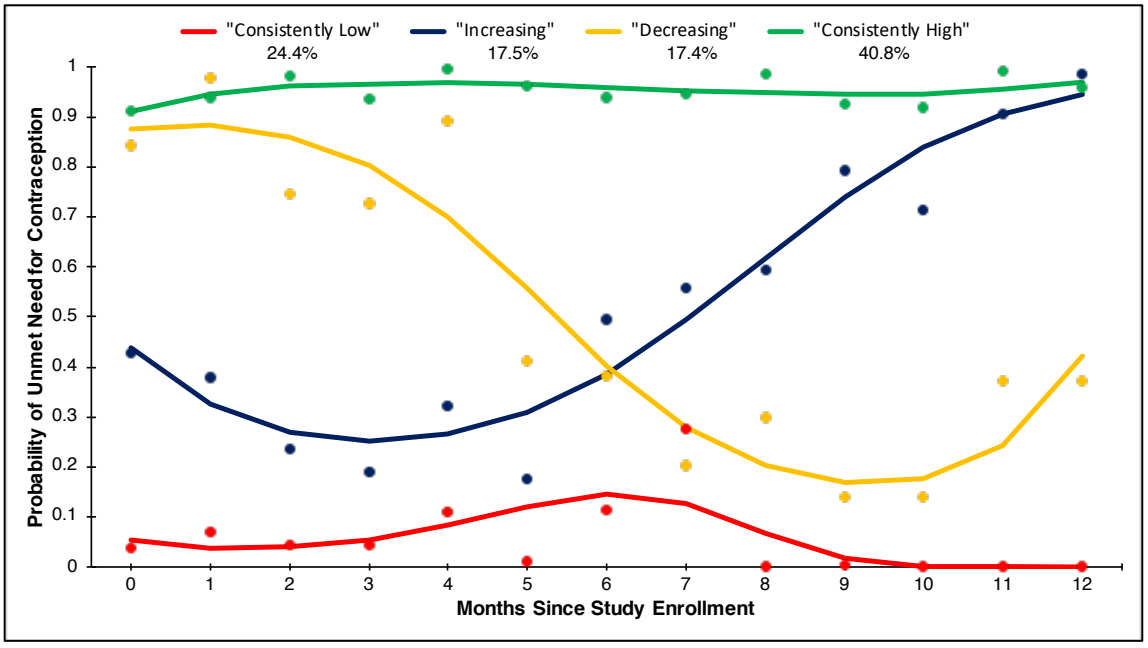
† n=13

FIGURE 4.1 Predicted trajectories of unmet need for contraception among HIV-infected women taking ART in Johannesburg, 2009-2011

Panel A represents predicted trajectories for the four-group quadratic model estimated for the full cohort (N=850). **Panel B** represents predicted trajectories for the four-group cubic model estimated for recent initiators of ART (N=157). Dots represent the observed proportion of women with unmet need for contraception among those assigned to a given trajectory group on the basis of their maximum posterior group membership probability. Curves represent the proportion of women with unmet need for contraception as estimated by the model for a given trajectory group.



A



B

FIGURE 4.2 Fertility intentions and contraceptive use over time, stratified by assigned trajectory group based on each participant's highest posterior group-membership probability for the full cohort (N=850)

At each monthly assessment women were either 1) not married, co-habitating, or sexually active, 2) trying to conceive, 3) using a reliable method of contraception to prevent pregnancy (contraceptive users) and 4) not using a reliable method of contraception to prevent pregnancy (those with unmet need for contraception).

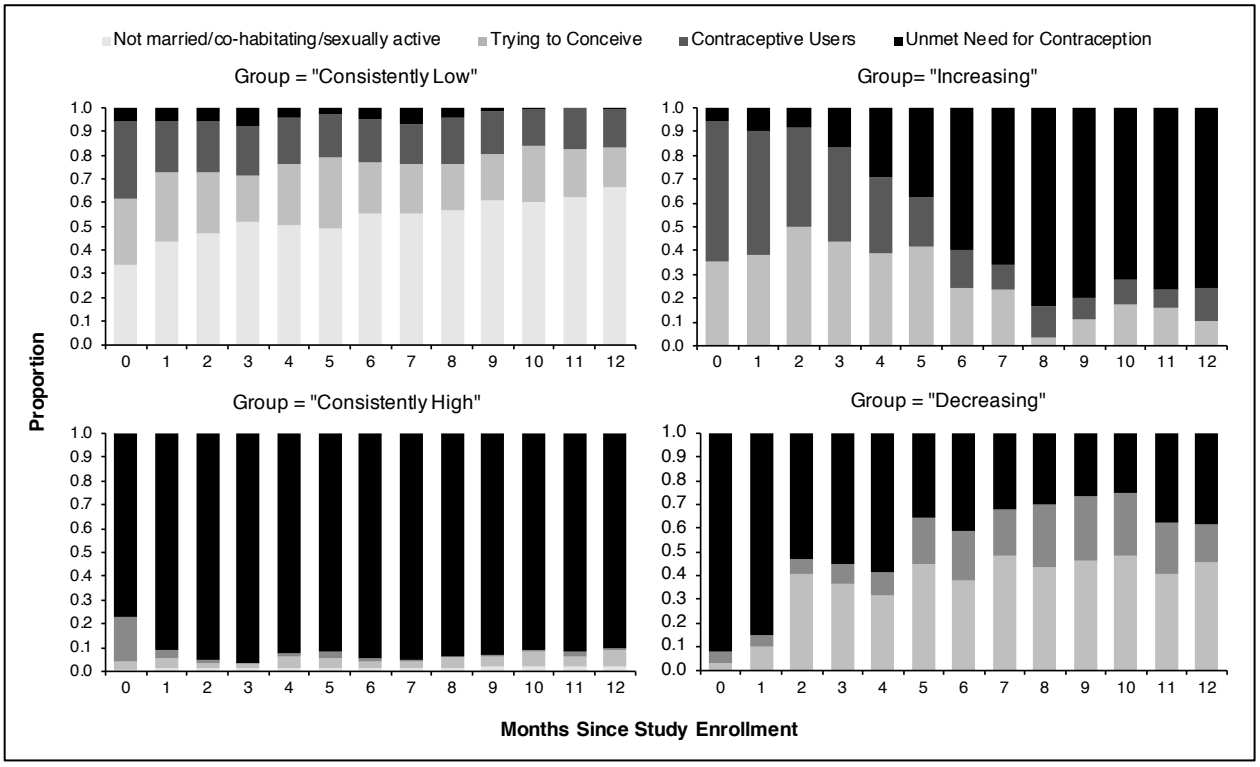
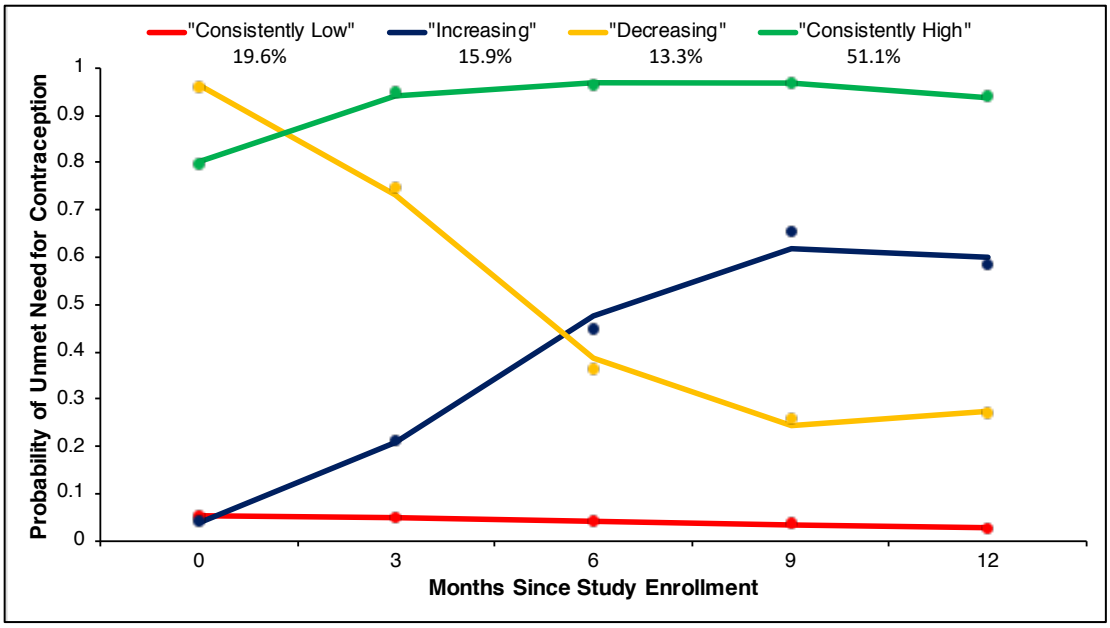


FIGURE 4.3 Predicted trajectories of unmet need for contraception using quarterly measurements among HIV-infected women taking ART in Johannesburg, 2009-2011. **Panel A** represents predicted trajectories for the four-group cubic model estimated for the full cohort (N=850) with unmet need for contraception assessed every three months. **Panel B** represents predicted trajectories for the four-group cubic model estimated for recent initiators of ART (N=157) with unmet need for contraception assessed every three months. Dots represent the observed proportion of women with unmet need for contraception among those assigned to a given trajectory group on the basis of their maximum posterior group membership probability. Curves represent the proportion of women with unmet need for contraception as estimated by the model for a given trajectory group.



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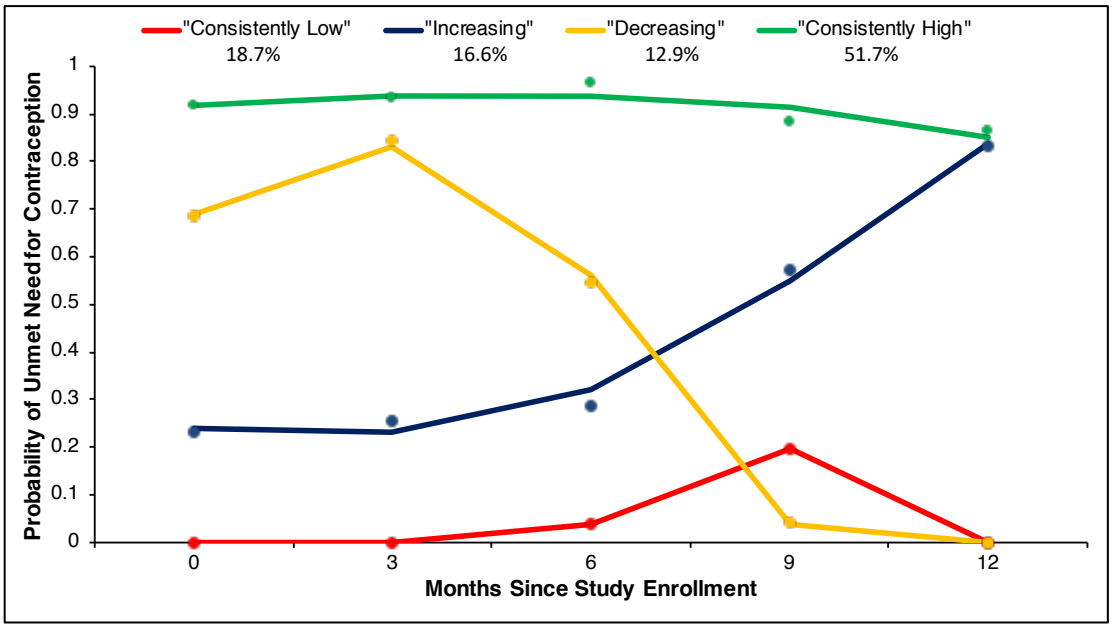
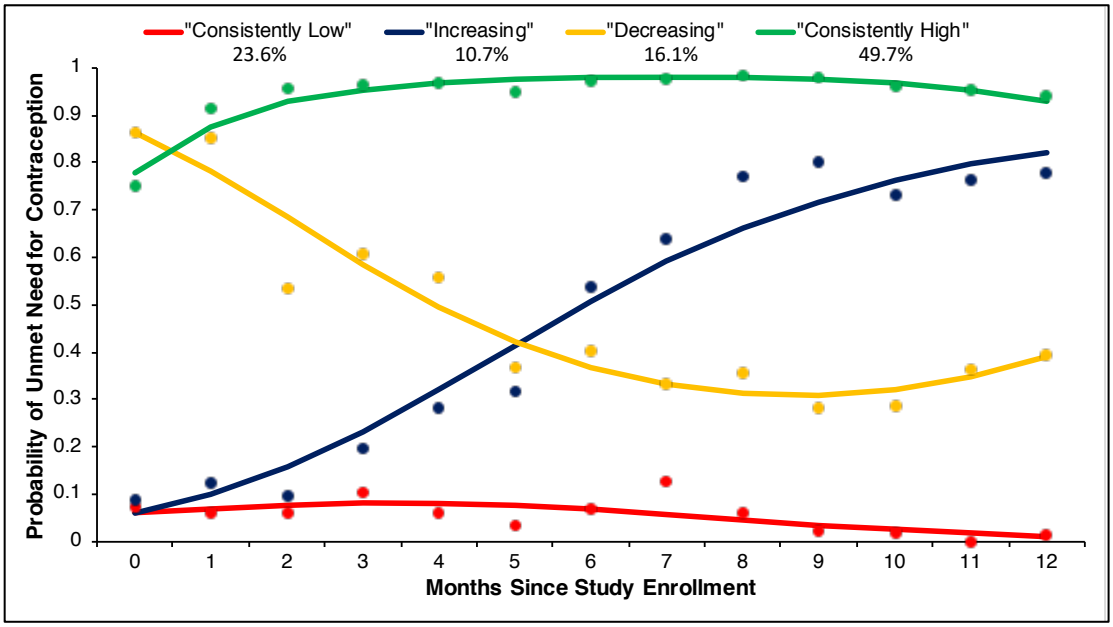


B

FIGURE 4.4 Predicted trajectories of unmet need for contraception among non-pregnant HIV-infected women taking ART in Johannesburg, 2009-2011.
Trajectories are presented for the four-group quadratic model estimated for women who did not become pregnant during the 12-month follow-up period (N=701). Dots represent the observed proportion of women with unmet need for contraception among those assigned to a given trajectory group on the basis of their maximum posterior group membership probability. Curves represent the proportion of women with unmet need for contraception as estimated by the model for a given trajectory group.



CHAPTER V: AIM 2

The effect of fertility intentions on attendance at HIV clinical care visits among HIV-infected women on antiretroviral therapy in South Africa

1. Introduction

Nearly 3.4 million people in South Africa are accessing lifesaving antiretroviral therapy (ART), making South Africa's national ART program the largest in the world.[36] In 2016, South Africa scaled up ART coverage by expanding ART eligibility for all persons living with HIV, irrespective of CD4 cell count.[122] Through this ambitious universal test and treat (UTT) initiative and guided by UNAIDS 90-90-90 targets,[123] South Africa aims to significantly reduce HIV-associated mortality and the number of new infections by 2020. The extent to which South Africa can meet these targets will depend on maximizing the proportion of those with HIV who sustain virologic suppression through care attendance and treatment adherence in the period following diagnosis.

ART offered through Option B+ has been available in South Africa to all women who are pregnant or breastfeeding since early 2015,[76] but challenges persist keeping women engaged in care during pregnancy and the postpartum period. ART coverage is substantially higher in HIV-infected women than in men in South Africa,[36] but significant concerns around adherence and retention have emerged around women who obtain treatment through Option B+.[77-79] Several studies have reported poor adherence and high rates of loss to follow-up (LTFU) or attrition from care among women who initiate ART during pregnancy compared to women who initiate ART for their own health,[26,27,29] especially in the postpartum period.[28,80,81] While factors that cause women to disengage from HIV care are complex and dynamic,[77] some have hypothesized that

women who initiate ART through PMTCT may be less motivated to remain in care in the postpartum period after the risk of mother-to-child transmission has decreased.[24,28,82]

One factor that that may influence engagement in care- both in the preconception and postpartum periods- is decision making around childbearing. Women who are planning to conceive have different clinical needs than those what wish to prevent pregnancy,[124] precipitating potential differences in the frequency with which women attend HIV clinical care visits. Concerns about horizontal transmission in the periconception period[125,126] or mother-to-child transmission[9] after conception may also motivate women who are planning to conceive to have a more consistent relationship with HIV care. Evidence distinguishing different HIV care patterns among women trying and not trying to conceive could potentially inform new models for care delivery the preconception period. Here, we estimated the effect of fertility intentions on attendance at HIV clinical care visits in the preconception period among HIV-infected women on ART in Johannesburg, South Africa.

2. Methods

2.2 Study Setting, Population and Procedures

This is a secondary analysis of data from a prospective cohort study conducted in Johannesburg between 2009 and 2011 originally designed to estimate the 12-month incidence of pregnancy in HIV-infected women on ART. Full study procedures and eligibility criteria have been published elsewhere.[5,32,33] In brief, all non-pregnant, sexually active women between the ages of 18 and 35 were eligible for participation if they had not delivered a pregnancy in the last three months; were not breastfeeding, had not had a previous tubal ligation, hysterectomy, or bi-lateral oophorectomy; and had not been diagnosed as permanently infertile. Pregnancy was assessed using urine-based tests administered by study staff (One Step hCG Urine Pregnancy Test, Atlas Link Technology, Beijing) and confirmed through repeat testing. After providing written informed consent, women meeting eligibility criteria completed an interviewer-administered questionnaire to assess demographic and behavioral characteristics including

fertility history and intentions, contraceptive use, and sexual risk behaviors. ART regimen information, CD4 cell count and viral load data were confirmed through medical record review, pharmacy and laboratory records. Follow-up visits coincided with regular clinic visits, every 1-3 months based on clinic protocol and provincial ART supply. During follow-up visits, women were tested for pregnancy and HIV-associated clinical outcomes were updated. Contraceptive use and fertility intentions were assessed using a short questionnaire at each follow-up visit.

2.3 Outcome and Exposure Assessment

To estimate the effect of fertility intentions on attendance at HIV clinical care visits, we constructed an analytic cohort in which each woman was followed from study enrollment through the completion of 12 months of follow-up or until date of censoring if she died, became pregnant or was known to have transferred to another clinic. We partitioned the 12-month follow-up period following enrollment into four discrete three-month intervals (quarters). Attendance at HIV clinical care visits was assessed dichotomously in each quarter; a woman was flagged as having attended a visit in a given interval if she attended one or more routine HIV clinical care visits in that interval (yes/no).

Fertility intentions were measured at enrollment using three questions that asked about current and future fertility intentions. Women were first asked if they were trying to conceive at time of interview (yes/no). Those that said no or were uncertain were then asked if they were planning to conceive in the next 12 months (yes/no/uncertain). Those that said no or were uncertain were then asked if they were planning to conceive someday in the future (yes/no/uncertain). In main analyses, women were then classified as having either current fertility intentions (trying at time of interview), short-term fertility intentions (planning to conceive in the next 12 months), long-term fertility intentions (planning to conceive in the future), or having no plans to conceive. Women who were uncertain about conceiving in the next 12 months who had plans to conceive in the future were classified as having long-term fertility

intentions and not short-term fertility intentions, and women who were uncertain about their long-term fertility intentions were grouped with women with no plans to conceive.

In additional analyses, we assessed the effect of time-varying fertility intentions on attendance at HIV clinical care visits. Women were asked if they were trying to conceive at the time of each HIV clinical care visit (yes/no).

2.4 Statistical Analysis

Demographic and clinical characteristics of women at enrollment were described overall and by dichotomized fertility intentions (any plans to conceive vs. no plans to conceive) using proportions for categorical variables and medians for continuous variables. Generalized linear models with a logit link were used to estimate the association between each category of fertility intentions and attendance, using generalized estimating equations (GEE) with an exchangeable correlation structure to account for within-subject correlation (multiple intervals of attendance per woman).[127]

Multivariable models were used to adjust for covariates identified using causal directed acyclic graphs (DAGs). Confounders included for adjustment were measured at enrollment and included age, marital status, ART duration, partner fertility intentions, having prior children and having a provider that discouraged having a/another child. We opted not to control for contraceptive use in multivariable models, since use of hormonal contraception likely mediates the causal relationship between fertility intentions and HIV care attendance and adjustment might bias estimates of the total effects of the exposures.

In time-varying analysis, we included a time lag for fertility intentions whereby we assessed attendance in each interval among women who reported they were either trying or not trying to conceive in the previous interval. Among women who attended more than one clinical care visit within a three-month period (and subsequently had more than one assessment of fertility intentions in a given interval), we used exposure information from the first visit only. To account for missing exposure information among women who did not attend a clinical care visit

within a three-month period, we initially excluded these women from our analysis (complete case analysis). To assess the robustness of our findings, we used inverse probability weighting to account for missing exposure data in the full cohort.

We considered potential effect measure modification (EMM) by ART duration, age and CD4 count assessed at enrollment using two dichotomized measures of fertility intentions ((any plans to conceive vs. no plans to conceive) and (currently trying to conceive vs. not currently trying to conceive)). To assess EMM by ART duration, we compared women who had initiated ART within three months of study enrollment (recent initiators) with those that had been on ART for more than three months (ART experienced). Our cutoff of three months was used to approximate those who had started ART on or around the time of study entry. Age was categorized about the median of 30 years and CD4 count was categorized about of 200 cells/μl. To formally test for EMM, we included an interaction term between the dichotomized exposure of fertility intentions and each of the proposed modifiers. Interaction terms with Wald test statistic p-values of <0.10 were considered significant and stratified estimates were reported. We considered both the magnitude and precision of stratum-specific estimates when making a final determination of EMM.

To account for potential exposure misclassification of fertility intentions, we conducted additional analyses around women who were uncertain about their fertility intentions in the short term and the long term. All analyses were conducted using SAS statistical software (SAS, version 9.4, Cary, NC).

3. Results

We enrolled 850 women and followed them for 12 months between August, 2009 and March, 2011. Over the 12-month period, 149 women (17.5%) became pregnant and contributed a median of 6.2 months (IQR 4, 9) of follow-up before they were censored. Twenty-eight (3.8%) women did not return to care after their initial study visit. Women were approximately 30 years of age (IQR 27, 33) and less than half were married (378/850, 44.5%) (Table 1). Most (680/850,

80.0%) had previously been pregnant. Median time since HIV diagnosis was 24 months (IQR 12, 48), and median time since ART initiation was 13 months (IQR 5, 24).

Most (742/850, 87.3%) women were planning to conceive at some point; 12.4% (105/850) were trying to conceive at enrollment. Compared to women who had no plans to conceive, women who were planning to conceive were less likely to have been previously pregnant (590/680 (86.8%) vs. 184/184 (100.0%)), to be taking hormonal contraception (162/680 (23.8%) vs. 62/184 (36.5%)) and to have been pregnant at HIV diagnosis (197/680 (29.0%) vs. 74/170 (45.5%)). Women who were trying to conceive had, on average, fewer living children (median 1 child (IQR 0,1) vs. median 2 children (IQR 2,3)). HIV-associated outcomes were similar in both groups.

Figure 5.1 illustrates the observed proportion of women attending an HIV clinical care visit over 12 months of follow-up. The probability of attending a visit decreased from 93.2% at month 3 to 81.0% at month 12. Table 5.2 includes odds ratios (ORs) and adjusted odds ratios (aORs) for attendance by each category of fertility intentions. We found no difference in clinic attendance by fertility intentions (comparing each category with those that were not trying to conceive) in unadjusted and adjusted models (Table 5.2). We similarly found no effect when we considered time-varying fertility intentions (Table 5.3). Results for sensitivity analyses where we classified women with uncertain fertility intentions as either not trying or trying to conceive in the short- and long-term were similar.

Table 5.4 summarizes the different effect estimates stratified by each potential effect measure modifier. There did not appear to be modification by ART duration, age, or CD4 count when we compared women who were currently trying to conceive with those who were not trying to conceive at enrollment. Stratum specific estimates differed, however, when we compared women with any plans for conception with those women who had no plans to conceive. Among women who had recently initiated ART, those that planned to conceive were more likely to attend HIV clinical care visits (aOR 2.95, 95% CI: 1.19, 7.30) than those with no

plans to conceive; however, precision was limited. Among women with a CD4 count of 200 or less, those that planned to conceive were more likely to attend HIV clinical care visits (aOR 2.31, 95% CI: 1.21, 4.41) than those with no plans to conceive.

4. Discussion

In this study of South African HIV-infected women taking ART, we observed a high probability of attendance at HIV clinical care visits over a 12-month period. We expected that women with plans to conceive in the short term would demonstrate greater engagement in care than those not planning a pregnancy. In fact, we observed comparable engagement overall between these groups. Subgroup analyses suggested that in women who recently initiated ART and among those with a low CD4 count at study enrollment, plans for pregnancy were associated with high attendance at HIV clinical care visits. To our knowledge, no other studies have previously assessed the relationship between fertility intentions and retention in HIV care.

There are several reasons why women who are planning to become pregnant may have a more consistent relationship with HIV clinical care at ART initiation than those with no plans for childbearing. In HIV-infected women, maternal concerns around mother-to-child transmission are thought to motivate care attendance during pregnancy.[9,11,24,28,30] It could be that pregnancy planners exhibit similar health-seeking behaviors in the preconception period. Concerns about horizontal transmission to HIV-uninfected partners during attempts to become pregnant may also prompt better attendance at HIV clinical care visits,[125,126] though data included in this analysis preempted wide understanding of treatment as prevention.[128]

We did not find an association between fertility intentions and care attendance in our full cohort, which included women with diverse ART experience at time of study entry. Women who are new to care and treatment may have greater HIV treatment optimism than those that are ART experienced, which may have motivated more frequent attendance for those with childbearing plans. Additionally, as our study's origin coincided with study entry and not with another biologically meaningful origin (e.g., HIV diagnosis, linked to care, ART initiation),[130]

women who chose to participate must have previously been retained in care up until the point of study entry. For example, women who initiated ART >1 year prior to study entry must have remained engaged in care up until the start of follow-up to be included in the cohort. Conversely, women who initiated ART at study entry did not have the same requirements for retention because the start of their follow-up period coincided with their entry into the study. We suspect that women in our study with a longer history of ART experience were innately better about attending HIV care visits overall, and that effect estimates for the full cohort may have been may diluted.[108]

Our analyses had several limitations. First, this study covered a 12-month period, which precluded us from assessing differences in LTFU or other long-term measures of care engagement. Consistent with other reported short-term estimates of retention in South Africa,[120] overall attendance in our study remained high (>80%) at the end of 12 months. This likely limited the precision of our effect estimates. Second, measures of fertility intentions included in this analysis may not reflect ambivalence around childbearing,[131] and women in our study may have misreported their plans for pregnancy. A strength of this study, however, was our use of prospectively collected measures of fertility intentions that preceded pregnancy, which may have reduced potential exposure misclassification.[132] Third, we were unable to assess the effect of fertility intentions on treatment adherence in our cohort, and while we assume that women who frequently attended care were also adherent to their ART, this may not be the case. Finally, at the time of study enrollment, non-pregnant women were only eligible for lifelong ART initiation with a CD4 count ≤200 cells/μl cells/ml or WHO clinical stage 4 diagnosis, and thus the generalizability of our study findings may be limited.[133] While we acknowledge this limitation, we believe these population-level differences to be incremental. Nevertheless, future research is needed to explore how fertility intentions affect care engagement among women initiating ART through UTT.

Despite these limitations, our findings suggest that fertility intentions impact care attendance in some women, and that novel strategies are needed to keep women without plans for conception retained in HIV care. Prioritizing PMTCT in already pregnant women has been widely successful in South Africa, reducing transmission during pregnancy to less than 3%.[36] As we enter a new era of HIV care and treatment, developing alternative models of care delivery that consider the diverse reproductive needs of HIV-infected women should be made a top priority.

5. Tables and Figures

TABLE 5.1 Characteristics at enrollment of 850 HIV-infected women taking ART in Johannesburg by dichotomized fertility intentions, 2009-2011

	Overall N=850 (100.0%)		Any plans to conceive N=680 (80.0%)		No plans to conceive N=170 (20.0%)	
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Age (years)	30.4	27-33	29.9	27-33	31.8	29-34
No. living children	1.0	1-2	1.0	0-2	2.0	2-3
Months since HIV diagnosis	24.0	12-48	24.0	12-48	28.0	12-48
CD4 count, cells/µl	312.0	178-462	302.0	175-459	345.0	217-468
HIV Viral load, copies/ml*	49.0	49-58	49.0	49-78	49.0	49-49
Months on ART	13.2	5-24	13.0	5-24	13.3	6-25
	n	**%**	**n**	**%**	**n**	**%**
Employed	510	60.0	402	59.2	108	63.5
Married/cohabitating	378	44.5	302	44.4	76	44.7
Ever pregnant	760	89.4	590	86.8	170	100
Trying to conceive, currently	105	12.4	105	15.4	0	0
Taking hormonal contraception	224	26.4	162	23.8	62	36.5
Pregnant at HIV diagnosis	271	31.9	197	29.0	74	45.5
Recruitment site						
ART initiation site	325	38.2	235	34.6	90	52.9
ART down-referral site	525	61.8	445	65.4	80	47.1

Abbreviations; IQR: Interquartile Range, No: Number, ART: Antiretroviral therapy, PMTCT: Prevention of month-to-child transmission

* n=834

TABLE 5.2 Unadjusted and adjusted Odds Ratios for the effect of fertility intentions on attendance at HIV clinical care visits

	No. (%)	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Categorical Fertility Intentions			
Current Fertility Intentions	170 (12.4)	0.80 (0.45, 1.42)	0.95 (0.51, 1.76)
Short-Term Fertility Intentions	291 (34.2)	0.86 (0.54, 1.37)	1.00 (0.61, 1.65)
Long-Term Fertility Intentions	284 (33.4)	1.13 (0.70, 1.80)	1.26 (0.77, 2.04)
No plans to conceive	170 (20.0)	1	1

Abbreviations. No.: Number, OR: Odds Ratio; CI: Confidence Interval

* Models were adjusted for a minimally sufficient set of confounders including age (≤30, >30), marital status (yes/no), time on ART (initiated ART ≤ 3 months, initiated ART >3 months), partner fertility intentions (no partner, partner does not desire a/another child, partner unsure, partner desires a/another child), any prior living children (yes/no), and provider discouraged future childbearing (yes/no).

TABLE 5.3 Unadjusted, adjusted and weighted Odds Ratios for the effect of time-varying fertility intentions on attendance at HIV clinical care visits

	No. (%)*	Unadjusted OR (95% CI)	Adjusted† OR (95% CI)	Weighted‡ OR (95% CI)
Time-varying fertility intentions				
Trying to conceive	105 (12.4)	0.89 (0.62, 1.28)	0.94 (0.64, 1.38)	0.89 (0.56, 1.44)
Not trying to conceive	745 (87.7)	1	1	1

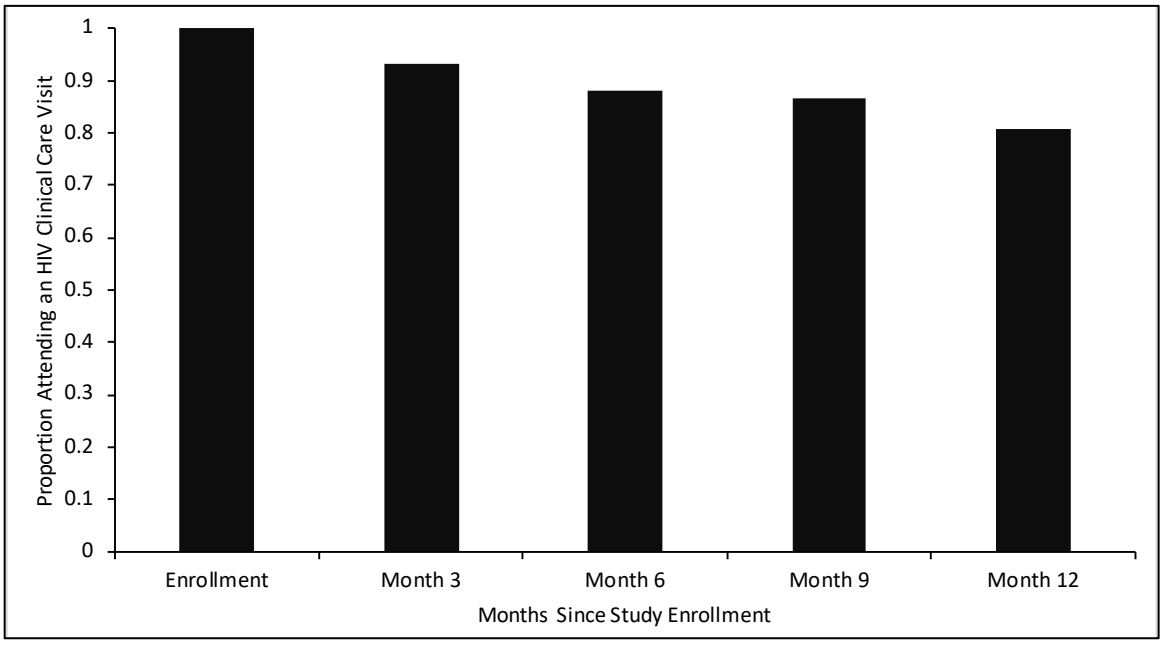
Abbreviations. No.: Number, OR: Odds Ratio; CI: Confidence Interval
* Proportion of those trying and not trying to conceive at enrollment
† Models were adjusted for a minimally sufficient set of confounders including age (≤30, >30), relationship status (yes/no), time on ART (initiated ART ≤3 months, initiated ART >3 months), partner fertility intentions (no partner, partner does not desire a/another child, partner unsure, partner desires a/another child), any prior living children (yes/no), and provider discouraged future childbearing (yes/no).
‡ Inverse-probability weighted effect estimates accounted for the following covariates: study visit, CD4 count, time on ART (initiated ART ≤3 months, initiated ART >3 months), employment status, and social grant status.

TABLE 5.4 Adjusted Odds Ratios for attendance at quarterly HIV clinical care visits over 12 months of follow-up, stratified by age, ART duration and CD4 count

Analysis Description	No. (%)	aOR* (95% CI)	
		Currently Trying to Conceive†	Any Plans to Conceive‡
Original (dichotomous)		0.94 (0.64, 1.38)	1.09 (0.70, 1.70)
Modification by ART duration			
Recent initiator	157 (18.5)	0.71 (0.30, 1.69)	2.95 (1.19, 7.30)
ART experienced	693 (81.5)	0.96 (0.53, 1.76)	0.94 (0.56, 1.60)
Modification by age			
≤30	523 (61.5)	0.78 (0.41, 1.45)	1.27 (0.74, 2.20)
>30	327 (38.5)	1.10 (0.50, 2.42)	0.98 (0.41, 2.34)
Modification by CD4 count			
≤200 cells/μl	405 (47.7)	0.87 (0.41, 1.85)	2.31 (1.21, 4.41)
>200 cells/μl	445 (52.4)	0.86 (0.46, 1.63)	0.74 (0.41, 1.33)

Abbreviations. No.: Number, OR: Odds Ratio; CI: Confidence Interval
* Models were adjusted for a minimally sufficient set of confounders including age (≤30, >30), relationship status (yes/no), time on ART (initiated ART ≤ 3 months, initiated ART >3 months), partner fertility intentions (no partner, partner does not desire a/another child, partner unsure, partner desires a/another child), any prior living children (yes/no), and provider discouraged future childbearing (yes/no).
† vs. those that were not trying to conceive
‡ vs. those with no plans to conceive

FIGURE 5.1 Probability of attendance at quarterly HIV clinical care visits over 12 months of follow-up



CHAPTER VI. DISCUSSION

1. Summary of Findings

The overall goal of this research was to better define the family planning needs of HIV-infected women within the context of HIV clinical care. We conducted our analyses using a rich and unique longitudinal cohort of 850 HIV-infected women who were previously on or being initiated onto ART in Johannesburg, South Africa.

In **Aim 1,** we assessed longitudinal patterns of unmet need for contraception over a 12-month period using group-based trajectory models. We found that more than 10% of women in our full cohort and nearly a quarter of those recently initiating ART were predicted to have unmet need that increased over time, indicating they were at higher risk of unintended pregnancy as time under observation increased. Our findings indicate that even within a 12-month period women's family planning needs may change rapidly, and that a single assessment of contraceptive need is insufficient in identifying those at high risk for unintended pregnancy.

In **Aim 2**, we estimated the effect of fertility intentions on HIV clinical care visits over a 12-month period. We found that the overall probability of attending a visit decreased from 93.2% at month 3 to 81.0% at month 12. In main analyses, we found no difference in clinic attendance by fertility intentions in unadjusted and adjusted models. Among women who had recently initiated ART, those that planned to conceive were more likely to attend HIV clinical care visits (aOR 2.95, 95% CI: 1.19, 7.30) than those with no plans to conceive; however, precision was limited. Among women with a CD4 count of 200 or less, those that planned to conceive were more likely to attend HIV clinical care visits (aOR 2.31, 95% CI: 1.21, 4.41) than those with no plans to conceive. Our findings demonstrate that targeted interventions may be needed to

promote engagement in HIV care for women who are not planning to become pregnant in the immediate period following ART initiation.

2. Contributions

Results from this study provide much-needed insights into the sexual and reproductive health of HIV-infected women taking ART in South Africa. To our knowledge, our study is the first to show that among HIV-infected women, trajectories of unmet need are dynamic – potentially increasing or decreasing – over a 12-month period. However, in current clinical practice, fertility intentions and contraceptive use are infrequently assessed in the context of HIV care. Consequently, women with unmet need for contraception may not be appropriately identified as being "at risk" for unintended pregnancy. Notably, among women in our study who were predicted to have an increasing probability of unmet need for contraception, only 6% were screened has having unmet need for contraception at enrollment. Without intervention, it's likely that these women went on to experience an unintended pregnancy.

While current national service delivery guidelines promote the integration of sexual and reproductive health services with HIV prevention, care and treatment in South Africa,[40] implementation of these guidelines in clinical practice has been limited.[41,37] Routine HIV clinical care visits represent a potential opportunity to regularly screen for family planning needs, particularly among women who do not realize they are able conceive after experiencing sub-fertility related to HIV-associated disease progression.[64-66] Furthermore, regularly assessing the family planning needs of women who have trouble achieving viral suppression is critical for both prevention of horizontal transmission to HIV-uninfected partners and PMTCT. Our findings further suggest that programs that include comprehensive screening for fertility intentions (for women and their partners), increase awareness about contraceptive side effects and method options, and provide high-quality training on contraceptive methods and safer conception will be most effective in decreasing unmet need for contraception in HIV-infected women.

Our study has also contributed to an understanding of how childbearing decisions affect a woman's relationship with HIV care. To our knowledge, no other studies have previously assessed the relationship between fertility intentions and retention in HIV care outside of the pregnancy period. While we did not detect an association between fertility intentions and attendance in the full cohort, we found that positive fertility intentions were associated with high attendance at HIV clinical care visits among women that had recently initiated ART.

Our findings have practical implications for HIV care delivery. For women with plans to conceive, our results demonstrate that HIV clinical care visits are an optimal space within which to offer safer conception services. We strongly advocate that comprehensive screening for fertility intentions- for both women and their partners- be prioritized to expand uptake of safer conception in this population. Sub-optimal attendance at HIV clinical care visits among women without plans to conceive is particularly troubling, as many women in this region often conjointly access contraception through HIV care and treatment. Our findings suggest that new models of care delivery that target women who wish to prevent or delay childbearing are urgently needed to simultaneously improve engagement in care and reduce the burden of unintended pregnancies in this population.

3. Limitations

Our study was not without several limitations. First, unmet need for contraception is derived from measures of fertility intentions and contraceptive use that are subject to potential outcome misclassification consistent with data collected by self-report. Self-reported contraception use may be subject to social desirability bias,[134] and binary measures of fertility intentions may be ambiguous and fail to capture ambivalence about conception and future pregnancy status.[135,136] Because all analyses for **Aim 1** were predictive and are without a defined causal question, we anticipate that potential misclassification of unmet need for contraception did not bias the interpretation of our findings. A strength of this study, however, was our use of prospectively collected measures of fertility intentions that preceded pregnancy,

which may have reduced potential exposure misclassification.[132] For **Aim 2**, our findings were robust to different exposure classifications of fertility intentions that accounted for potential uncertainty around childbearing. Nevertheless, as these analyses were causal, we acknowledge potential exposure misclassification as a limitation of this analysis.

Second, as identified by our DAG, pregnancy is a causal intermediate on the pathway between fertility intentions and retention in care for **Aim 2.** This relationship likely manifests because of maternal concerns regarding fetal health and mother-to-child transmission, and because women may first present to care after receiving a positive HIV diagnosis through antenatal testing. While we anticipate a woman's relationship with care changes after she becomes pregnant, our interest in this study lied more in estimating the total effect of fertility intentions prior to pregnancy on retention in care.

Third, at study entry, eligible women were either on or being initiated onto ART, and subsequently differences in developmental trajectories for unmet need may differ by time-on-ART. Our investigation primarily focused on characterizing trajectories of unmet need for contraception in a real-world population of HIV-infected women engaged in HIV care, and our study design is indicative of the reality in which women are seen and counseled on contraception in the context of HIV clinical care. When we restricted analyses to those women that had recently initiated ART, however, trajectories were generally similar to those that emerged in the full cohort.

Fourth, as our study's origin coincided with study entry and not with another biologically meaningful origin (e.g., HIV diagnosis, linked to care, ART initiation),[130] women who chose to participate must have previously been retained in care up until the point of study entry. For example, women who initiated ART >1 year prior to study entry must have remained engaged in care up until the start of follow-up to be included in the cohort. Conversely, women who initiated ART at study entry did not have the same requirements for retention because the start of their follow-up period coincided with their entry into the study. We suspect that women in our study

with a longer history of ART experience were innately better about attending HIV care visits overall, and that effect estimates for the full cohort may have been may diluted.[108]

Fifth, study visits during the 12-month follow-up period occurred during clinic visits every 1-3 months based on clinic protocol and provincial ART supply, and we saw some differences in the number and frequency of study visits across participants. However, our selected analytic approaches for both **Aim 1 and Aim 2** accommodated differences in both the total number of observations the frequency of observations. For **Aim 1**, we repeated our analysis using quarterly assessments of unmet need for contraception (vs. monthly) to account for differences in study visits. For **Aim 2,** attendance at HIV clinical care visits was similarly measured every three months.

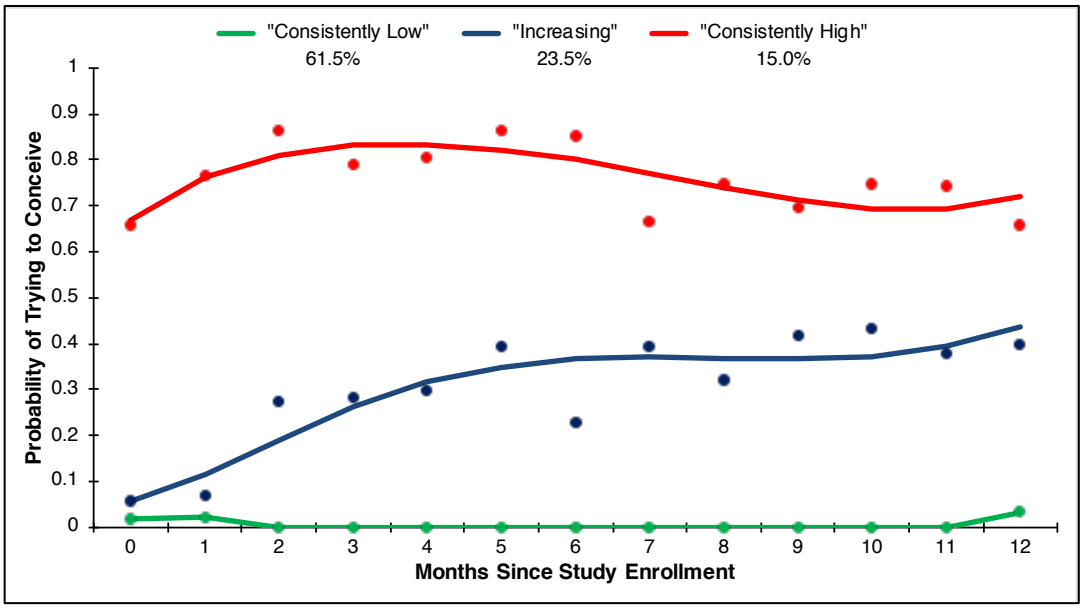
Finally, at the time of study enrollment, non-pregnant women were only eligible for lifelong ART initiation with a CD4 count ≤200 cells/μl cells/ml or WHO clinical stage 4 diagnosis, and thus the generalizability of our study findings may be limited. In **Aim 1**, trajectories of unmet need and predictors thereof may differ in the current era of expanded HIV care and treatment. However, we believe any differences to be incremental, as we saw little difference in CD4 count by trajectory group. Furthermore, trajectories were largely similar among recent ART initiators who started treatment for their own health. In **Aim 2**, women who initiate ART because of disease severity may be more likely to be retained in care compared to women who initiate ART during pregnancy. While we acknowledge these limitations to our analyses, we believe these population-level differences to be incremental overall. Notably, a recent study found that despite revised thresholds for ART initiation in sub-Saharan Africa, CD4 counts at presentation to care have not changed over the past ten years.[137] Thus, despite expanded availability of ART through UTT, we believe our study findings are generalizable to the current population of HIV-infected women living in South Africa.

4. Conclusions

Through this research we have provided a more nuanced understanding of the family planning needs of HIV-infected women. We have demonstrated that changing fertility intentions and contraceptive use inform dynamic patterns of unmet need for contraception over a 12-month period, and that women without plans for pregnancy may have a measurably inconsistently relationship with HIV care in the period following ART initiation. Our findings suggest that routine and comprehensive screening for fertility intentions within HIV clinical care visits is integral for prevention of unintended pregnancies in this population. As we enter a new era of HIV care and treatment, developing alternative models of care delivery that consider the diverse reproductive needs of HIV-infected women should be made a top priority.

APPENDIX 1. Supplementary Group-Based Trajectory Models for Fertility Intentions

Figure 1.1. Panel A represents predicted trajectories for the three-group cubic model estimated for the full cohort (N=850). **Panel B** represents predicted trajectories for the three-group quadratic model estimated for recent initiators of ART (N=157). Dots represent the observed proportion of women trying to conceive among those assigned to a given trajectory group on the basis of their maximum posterior group membership probability. Curves represent the proportion of women trying to conceive as estimated by the model for a given trajectory group.



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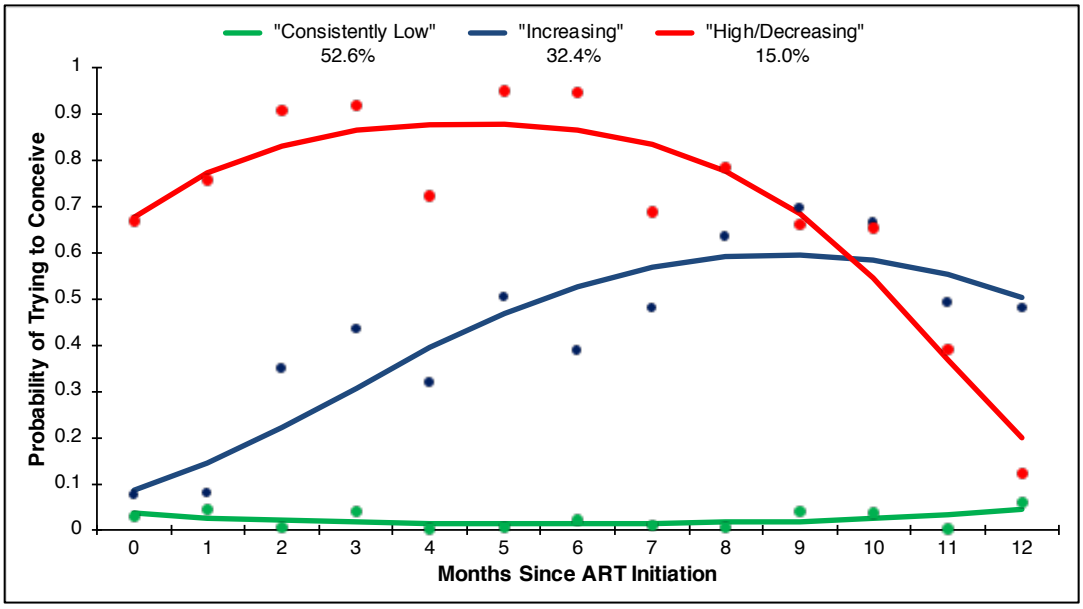

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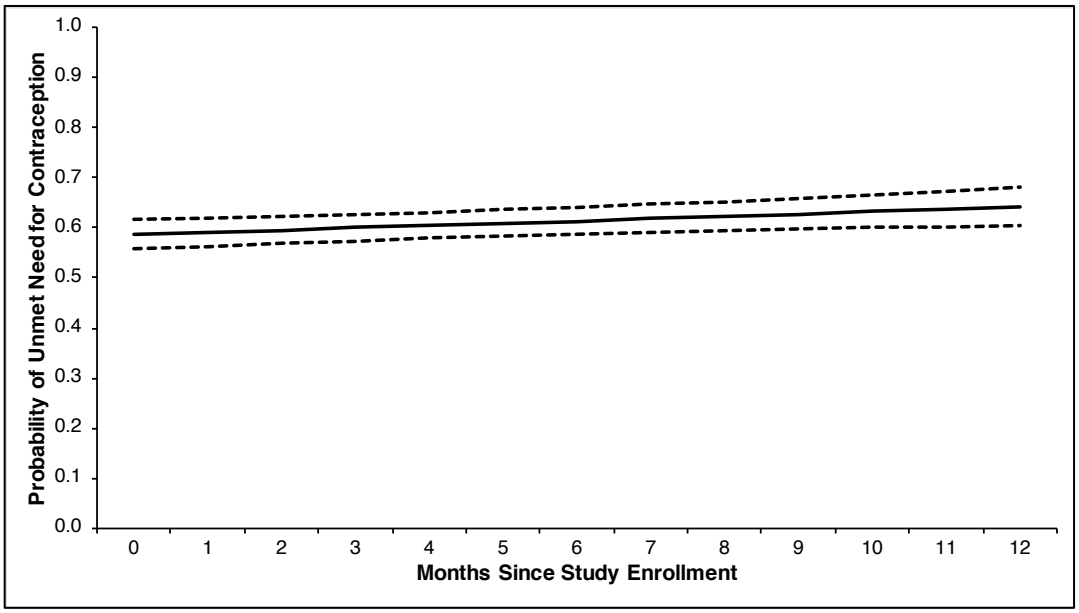
APPENDIX 2. Supplementary Analysis of Unmet Need for Contraception

Figure 2.1. Panel A represents predicted probability of having unmet need for contraception in the full cohort (N=850) over the study period; dashed lines represent upper and lower 95% confidence intervals. **Panel B** represents predicted probability of having unmet need for contraception in recent initiators (N=157). Log-binomial models were fit using generalized estimating equations (GEE) to with an exchangeable correlation structure to account for within-subject correlation.



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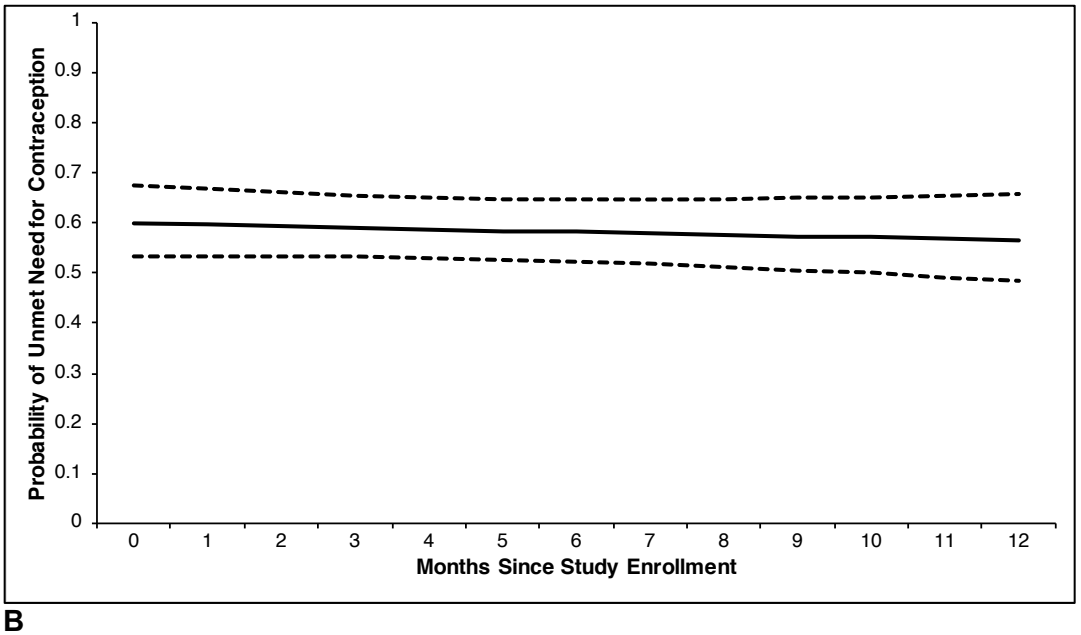

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